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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07K 5/02, 5/06, 5/08, A61K 37/02

A1

(11) International Publication Number: WO 94/24149

(43) International Publication Date: 27 October 1994 (27.10.94)

(21) International Application Number: PCT/EP94/01131

(22) International Filing Date: 14 April 1994 (14.04.94)

(30) Priority Data:
9307833.5 15 April 1993 (15.04.93) GB

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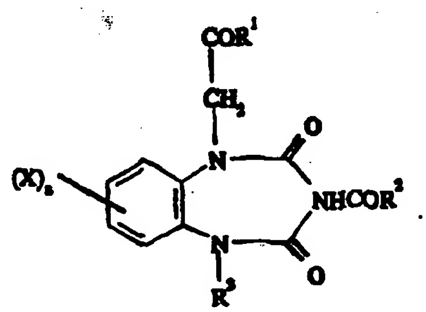
(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 1,5-BENZODIAZEPINE DERIVATIVES HAVING CCK ANTAGONISTIC OR AGONISTIC ACTIVITY

(57) Abstract

Novel benzodiazepine compounds of formula (1) which exhibit agonistic activity for CCK-A receptors enabling them to modulate the hormones gastrin and cholecystokinin (CCK) in mammals for use in medicine as anorectic agents in the regulation of appetite, the treatment of obesity and the maintenance of weight loss.



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1,5 -BENZODIAZEPINE DERIVATIVES HAVING CCK ANTAGONISTIC OR AGONISTIC ACTIVITY

This invention relates to novel 1,5-benzodiazepine derivatives, to process s for their preparation, to pharmaceutical compositions containing them and to their use in medicine. More particularly, it relates to compounds which exhibit agonist activity for CCK-A receptors thereby enabling them to modulate the hormones gastrin and cholecystokinin (CCK) in mammals.

Cholecystokinins (CCK) and gastrin are structurally related peptides which exist in gastrointestinal tissue and in the central nervous system. Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form, its carboxyl terminal octapeptide, CCK-8 (also a naturally occurring neuropeptide), and 39- and 12-amino acid forms. Gastrin occurs in 34-, 17- and 14- amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH_2 (CCK-4) which is the common structural element shared by both CCK and gastrin.

CCK and gastrin are gastrointestinal hormones and neurotransmitters in the neural and peripheral systems and perform their respective biological roles by binding to particular receptors located at various sites throughout the body. There are at least two subtypes of cholecystokinin receptors termed CCK-A and CCK-B and both are found in the periphery and in the central nervous system.

The CCK-A receptor, commonly referred to as the "peripheral-type" receptor, is primarily found in the pancreas, gallbladder, ileum, pyloric sphincter and on vagal afferent nerve fibers. Type-A CCK receptors are also found in the brain in discrete regions and serve to provide a number of CNS effects. Due to the ability of CCK-8 and Type-A CCK-selective agonists to suppress food intake in several animal species, considerable interest has been generated toward the development of new substances which function as Type-A receptor-selective CCK agonists in order to serve as anorectic agents.

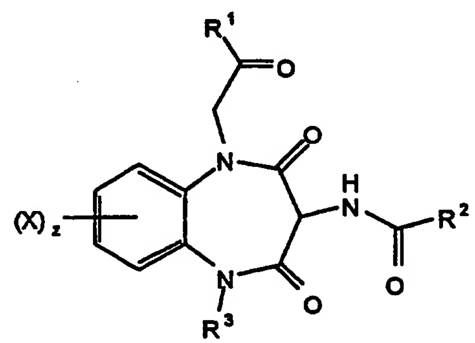
The CCK-B or gastrin receptors are found in peripheral neurons, gastrointestinal smooth muscle and gastrointestinal mucosa, most notably in parietal cells, ECL cells, D cells and chief cells. CCK-B receptors also predominate in th brain and have been implicated in the regulation of anxiety, arousal and the action of neuroleptic agents.

U.S. Patent No. 4,988,692, to Gasc, et al. describes a group of 3-acylamino 1-alkyl-5-phenyl 1,5-benzodiazepine derivatives which behav as cholecystokinin antagonists to reverse or block th ffects of the endogenous hormone at its receptors.

US Patent. No. 4,490,304 and PTC applications No's WO90/06937 and WO91/19733 describe peptide derivatives that exhibit CCK-A agonist activity. Such compounds have been disclosed for appetite regulation as well as the treatment and/or prevention of gastrointestinal disorders or disorders of the central nervous in animals and, more particularly, humans.

We have now discovered a novel group of 3-amino 1,5-benzodiazepine compounds which exhibit a agonist activity for the CCK-A receptor thereby enabling them to modulate the hormones gastrin and cholecystokinin (CCK) in mammals. Certain of these compounds also exhibit antagonist activity at CCK-B receptors.

The present invention thus provides compounds of the general Formula (I)

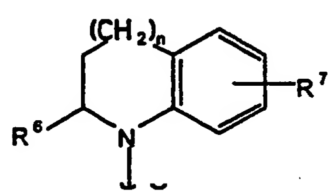


(I)

and physiologically salts and solvate thereof wherein:

X is either hydrogen, trifluoromethyl, alkyl, C_{1-4}alkylthio, -O(C_{1-4}alkyl) or halogen;

R^1 is either Formula II or -NR^4R^5.;



(II)

R^2 is eith r:

(1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrole, indole, benzofuran, thiophene, benzothiophene, indoline, quinoline or 4-oxobenzopyran and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R^8 as defined hereunder and said indole, indoline, quinoline, benzofuran, benzothiophene or 4-oxo-benzopyran may optionally be substituted in the benzo ring thereof by the group R^9 as defined hereunder or

(2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, $-O(C_{1-4}alkyl)$, $-O(CH_2C_6H_5)$, $-COO(C_{1-4}alkyl)$, amino, dimethylamino, $-NHR^{10}$, 1-pyrrolidinyl or tetrazolyl; or

(3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, $-O(C_{1-4}$ alkyl), $-O(CH_2C_6H_5)$, $-COO(C_{1-4}alkyl)$, amino or dimethylamino; or

(4) $-NHR^{11}$ where R^{11} is defined hereinunder or R^{11} is 7-indazolyl containing a group R^{10} at the N-1 position;

R^3 is hydrogen, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, phenyl or phenyl mono- or disubstituted independently with halogen;

R^4 is independently $C_{3-6}alkyl$, $C_{3-6}cycloalkyl$, $C_{3-6}alkenyl$, phenyl, $-(CH_2)_pCN$ or $-(CH_2)_pCOO(C_{1-4}alkyl)$ and R^5 is independently $C_{3-6}alkyl$, $C_{3-6}cycloalkyl$, C_{3-6} alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with $C_{1-3}alkyl$, cyano, hydroxy, dimethylamino, $-O(C_{1-4}alkyl)$, $-O(CH_2C_6H_5)$, $-NH(C_{1-4}alkyl)$, $-COO(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$ pyrrolidino, morpholino or halogen or R^4 is $C_{1-2}alkyl$ and R^5 is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;

R^6 is hydrogen or methyl;

R^7 is hydrogen, hydroxy, fluoro, dimethylamino, $-O(C_{1-4}alkyl)$ or $-O(CH_2C_6H_5)$;

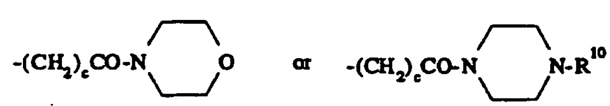
R^8 is $-(CH_2)_bCOOH$;

R^9 is methyl, chloro, nitro, hydroxy, methoxy or $-NHR^{10}$;

R^{10} is hydrogen, acetyl, C_{1-4}alkyl, $-SO_3H$, $-SO_2CH_3$, $-SO_2CF_3$ or $-SO_2C_6H_5$, C_{1-4}alkoxycarbonyl;

R^{11} is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C_{1-4}alkylthio, $-(CH_2)_cCOOH$, $-(CH_2)_cCOO(C_{1-4}alkyl)$, $-(CH_2)_cSCH_3$, $-(CH_2)_cSOCH_3$, $-(CH_2)_cSO_2CH_3$, $-(CH_2)_cCONH_2$, $-SCH_2COOH$, $-CONH(SO_2CH_3)$, $-CONH(SO_2CF_3)$, $-(CH_2)_cN(C_{1-4}alkyl)_2$, $-(CH_2)_cNH(SO_2CF_3)$, $-(CH_2)_cN(SO_2CF_3)(C_{1-4}alkyl)$, $-(CH_2)_cSO_2NHCO(C_{1-4}alkyl)$, $-(CH_2)_cSO_2N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $-(CH_2)_cCONHSO_2(C_{1-4}alkyl)$, $-(CH_2)_cCON(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-(CH_2)_cOR^{12}$ $-(CH_2)_cNHR^{10}$ or phenyl monosubstituted with $-(CH_2)_c$(tetrazolyl), $-(CH_2)_c$(carboxamidotetrazolyl) or $-(CH_2)_c$(pyrrolidinyl) or R^{11} is selected from pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, $-O(C_{1-4}$ alkyl$)$, amino, dimethylamino, $-NHR^{10}$;

R^{12} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2C_6H_5$, $-CH_2COOH$, $-CH_2CONH_2$, $-CH_2CONH(C_{1-4}alkyl)$, $-CH_2CON(C_{1-4}alkyl)_2$ or



z is 1 or 2;

n is 1 or 2;

p is an integer from 1-4;

b is an integer from 0-3; and

c is 0 or 1.

When R^1 represents the group of Formula (II), examples of such a group include those wherein R^6 is hydrogen or more particularly m thyl, R^7 is hydrogen, hydroxyl, methoxy, or fluorine, and n is 1.

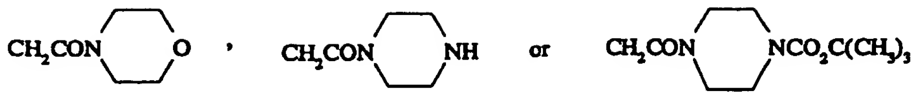
When R^1 represents the group NR^4R^5, examples of suitable groups include those wherein R^4 represent C_{3-6} alkyl, such as propyl or isopropyl, cyclohexyl or phenyl and R^5 represents C_{3-6} alkyl, benzyl or phenyl optionally substituted in the para- position by hydroxy, dimethylamino methoxy, fluorine, pyrrolidino or morpholino. Within this group, particularly useful R^1 groups include those wherein R^4 is propyl and, more particularly, isopropyl and R^5 represents phenyl or phenyl substituted in the para-position by groups selected from hydroxy, methoxy dimethylamino, fluorine, or morpholino.

Examples of particularly suitable R^1 groups include those wherein R^1 is the group of Formula (II) wherein R_6 is methyl, n is 1 and R^7 is hydrogen, hydroxy, fluorine or methoxy or R^1 is the group NR^4R^5 wherein R^4 is propyl or isopropyl and R^5 is phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, dimethylamino, pyrrolidino or morpholino.

When R^2 represents a group selected from indole, indoline, benzofuran, benzothiophene, quinoline or 4-oxobenzopyran, the optional substituent R^9 is conveniently a group selected from hydrogen, methyl, methoxy, hydroxy, nitro or amino and, where appropriate, the optional substituent on nitrogen, (R^8), is $-CH_2CO_2H$.

When R^2 is an optionally substituted phenyl group, this is conveniently phenyl or phenyl substituted by one or two groups, which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxyl.

When R^2 represents the group NHR^{11}, R^{11} is conveniently phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C_{1-4} alkoxycarbonyl, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein R^{12} represents hydrogen, methyl, benzyl, CH_2CO_2H, CH_2CONH_2, $CH_2CONHCH_3$, $CH_2CON(CH_3)_2$



) or a 7-indazolyl group wherein the N-1 substituent, (R^{10}), is hydrogen.

When R^{11} is a mono substituted phenyl group, the substituted is conveniently in the meta- position.

Examples of particularly suitable R^2 groups includes indole, benzofuran, thiophene, benzothiophene, indoline, quinoline, 4-oxobenzopyran, an optionally substituted phenyl group or the group NHR^{11}. Conveniently, R^2 is selected from the group indole, indoline or benzofuran, an optionally substituted phenyl group or the group NHR^{11}. More particularly, R^2 represents an indole, an optionally substituted phenyl or NHR^{11}.

When R_3 represents C_{1-6} alkyl, examples of suitable groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl or isoamyl.

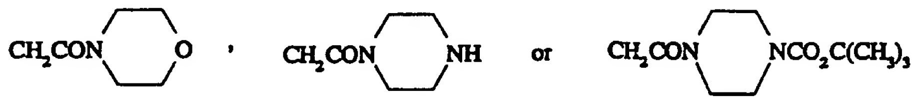
When R_3 represents C_{3-6} cycloalkyl, examples of suitable groups include cyclopropyl, cyclopentyl or cyclohexyl.

When R_3 represents phenyl, mono or disubstituted by independently with halogen, examples of suitable groups include those wherein the halogen substituent is fluorine e.g., 2-fluorophenyl or 4 fluorophenyl.

Examples of particularly suitable R^3 groups include hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl, and more particularly, phenyl.

A particularly useful group of compounds according to the invention include those wherein R^1 represents the group of Formula (II) wherein R^6 is methyl, n is 1 and R^7 is hydrogen, fluorine, hydroxy or methoxy, or more particularly NR^4R^5 wherein R^4 is propyl or isopropyl and R^5 is phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, dimethylamino or monopholino; R^2 represents phenyl (optionally substituted independently by one or two groups selected from chlorine, fluorine, hydroxy, amine or carboxy), NHR^{11} wherein R^{11} represents phenyl (optionally substitut d by amino, dimethylamino, trifluoromethylsulphonylamino, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein

R^{12} represents hydrogen, methyl, benzyl, CH_2CO_2H, CH_2CONH_2, $CH_2CONHCH_3$, $CH_2CON(CH_3)_2$,



and

wherein the substituent is preferably in the meta- position) or an indole wherein the nitrogen atom is optionally subtituted by the group $-CH_2CO_2H$ and the benzo ring is optionally substituted by chlorine, methyl, methoxy, nitro, hydroxy or amino; R^3 represents hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl or, more particularly, 2 fluorophenyl or phenyl; and X represents fluorine and z is 1 or, more particularly, X is hydrogen;

A particularly interesting class of compounds of the present invention which exhibits a very high and selective affinity for the CCK-A receptor as well as exceptional efficacy occurs wherein R^2 is an indole group. A preferred group of compounds within this class are those wherein the indole group is substituted on the nitrogen atom by the group $-CH_2CO_2H$ or, more preferably, the nitrogen atom is unsubstituted, and benzo ring of the indole group is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

A particularly preferred compound of the invention is:
1H-Indole-2-carboxylic acid {1-[Isopropyl-(4-methoxyphenyl)carbamoyl-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl}-amide and enantiomers thereof.

As provided herein, the term alkyl is generally intended to mean both straight chain and branched chain aliphatic isomers of the corresponding alkyl. For example, C_{1-6}alkyl is intended to include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertbutyl, n-pentyl, etc.

The term cycloalkyl, as provided herein, is intended to mean all alicyclic isomers of the corresponding alkyl. For example, the term C_{3-6} alkyl, as provided herein, is intended to include such groups as cyclopropyl, cyclopentyl and cyclohexyl.

The term halogen is intended to mean F, Cl, Br or I.

The term tetrazole as a group or part of a group refers to th (1 H)-tetrazol-5-yl grouping and tautomers thereof.

Those skilled in the art will recognize that stereocenters exist in compounds of Formula (I). Accordingly, the present invention includes all possible stereoisomers and geometric isomers of Formula (I) and includes not only racemic compounds but also the optically active isomers as well. When a compound of Formula (I) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Carbon Compounds by E. L. Eliel (Mcgraw Hill, 1962) and Tables of Resolving Agents by S. H. Wilen. Additionally, in situations where tautomers of the compounds of Formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds.

It will also be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts of the compounds of Formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids as well as quaternary ammonium acid addition salts. More specific examples of suitable salts include hydrochloric, hydrobromic, sulphuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, pamoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulphonic, methanesulphonic, naphthalene-2-sulphonic, benzenesulphonic and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. References hereinafter to a compound according to the invention include both compounds of Formula (I) and their pharmaceutically acceptable salts and solvates.

The compounds of the present invention exhibit CCK-A agonist activity and can be considered full or partial cholecystokinin agonists in that they bind to

CCK-A receptors and either fully or partially stimulate gallbladder contraction and/or reduce feeding in animal paradigms.

As agonists of CCK-A receptors, the compounds of the present invention are useful anorectic agents advantageous in the treatment of obesity as well as related pathologies, such as diabetes or hypertension. Moreover, the compounds disclosed herein provide for new approaches for inducing satiety, providing for appetite regulation and modifying food intake in mammals, especially humans, to regulate appetite, treat obesity and maintain weight loss.

Additionally, certain compounds of the present invention may also exhibit some antagonist activity at particular site-specific CCK-B and gastrin receptors as demonstrated by their inhibition of CCK-4 stimulated contraction of isolated guinea-pig ileum longitudinal muscle-myenteric plexus and pentagastrin-stimulated acid secretion in rat isolated gastric mucosa using the procedures described by M. Patel and C. F. Spraggs in Br. J. Pharmac., (1992), 106, 275-282 and by J. J. Reeves and R. Stables in Br. J. Pharmac., (1985), 86, 677-684.

The relavtive affinities of compounds of the invention for the CCK-A and CCK-B receptors may be determined using known conventional procedures such as described by Fornos et al J. Pharmacol Exp. Ther., 1992 261, 1056-1063.

The ability of compouds of the invention to inhibit gastric acid secretion, such as pentagastrin stimulated acid secretion may be determined in the conscrious gastric fistula rat using methods described by Hedges and Parsons Journal of Physiology 1977, 267 191-194.

In particular, the invention provides a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, and in particular, in human medicine.

According to another aspect, the present invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof for th manufactur of a medicament for th tr atment of conditions

where modification of the effects of CCK and/or gastrin is of therapeutic ben fit.

According to a further aspect of the present invention, there is provided herein a method for the treatment of a mammal, including man, in particular in the treatment conditions where modification of the effects of CCK and/or gastrin is of therapeutic benefit, the method comprising administering to the patient an therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02 - 5000 mg per day, e.g., 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that compounds of the present invention may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. Accordingly, the present invention further provides for a pharmaceutical formulation comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations of the present invention include those especially formulated for oral, buccal, parenteral, implant, or rectal administration, however, oral administration is preferred. For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner. Tablets and capsules for oral administration may contain conventional

excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fill rs (for example, lactose, sugar, microcrystalline cellulose, maiz -starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulphate. The tablets may be coated according to methods well-known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

Additionally, compositions the present invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle (e.g., sterile, pyrogen-free water) before use.

The composition according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (as an mulsion

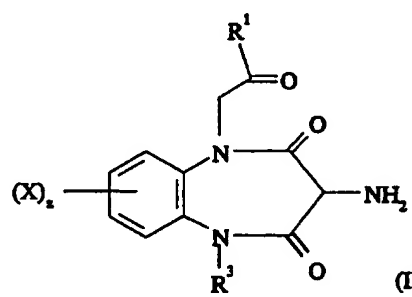
in an acceptable oil, for example), ion exchange resins or as sparingly soluble derivatives as a sparingly soluble salt, for example.

The compositions according to the invention may contain between 0.1 - 99% of the active ingredient, conveniently from 30 - 95% for tablets and capsules and 3 - 50% for liquid preparations.

Compounds of general Formula (I) may be prepared by the general methods outlined hereinafter. In the following description, the groups X and R^{1-12} are as defined for the compounds of Formula (I) unless stated otherwise.

Compounds of general formula (I) and salts thereof may be prepared by the general methods outlined hereinafter. In the following description, the groups R_1-R^{12} and X are as defined for the compounds of formula (I) unless otherwise stated.

According to a first general process A, compounds of formula (I) may be prepared by the reaction of an amine of formula (III) wherein R^1, R^2, R^3, X and z have the meanings defined in formula (I)



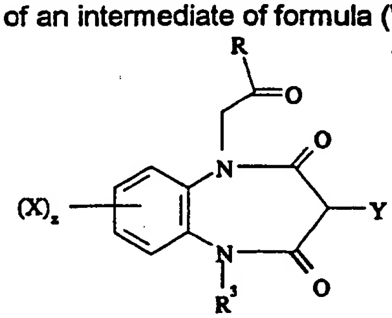
(III)

with a compound $R^{11}Y$ (IV) wherein Y is the group -NCO, HNCOCl or $NHCOR_a$ where R_a is nitro substituted phenoxy group or a 1-imidazole group.

The reaction conveniently takes place in the presence of a suitable solvent such as a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran) or nitrile (e.g. acetronitrile) or a mixture thereof at a temperature in the range of 0^0-80^0C.

Compounds of formula (IV) wherein Y is -NCO) may b purchased or prepared by the reaction of amines $H_2N\text{-}R^{11}$ with phosgene or triphosgene in a suitable solvent such as methylene chlorid . Compounds of formula (IV) wherein Yis NHCOCl are also prepared by the reaction of amines H_2NR^{11} with phosgene or triphosgene in a suitable solvent such as methylene chloride. Compounds of formula (IV) wherein Y is $NHCOR_a$ and R_a is a 1-imidazole group are prepared by treatment of amines $H_2N\text{-}R^{11}$ with carbonyl diimidazole in a suitable solvent (dichloromethane, ether, tetrahydrofuran) at a temperature ranging from 0-80° C (conveniently at room temperature). Compounds of formula (IV) wherein Y is $HNCOR_a$ and R_a is a nitro substitued phenxoy group are prepared by the reaction of amines $H_2N\text{-}R^{11}$ with the appropriate chloroformate R_aCOCl in the presence of a base (pyridine, triethylamine) in a suitable solvent (dichloromethane) and at a temperature of 0 - 50° C.

According to a further general process B, compounds of formula (I) may be prepared by reaction of an intermediate of formula (V).



(V)

wherein Y is the group -NCO, -NHCOCl or $NHCOR_a$ wherein R_a is a nitro substituted phenoxy group or a 1-imidazole group with an amine (VI)

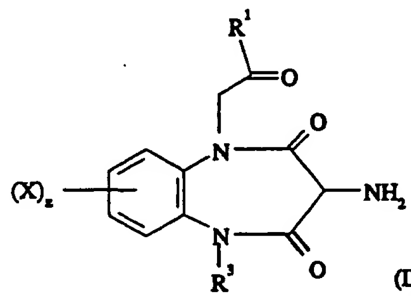
$$H_2N\text{-}R^{11} \qquad \text{(VI)}$$

and optionally in the the presence of a base such as a tertiary amine (e.g. triethylamine).

The reaction conveniently takes place in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an ether (e.g. tetrahydrofuran) or an amide (e.g. N,N-dimethyl formamide) optionally at a temperature ranging from room temperature to the reflux temperature of the solvent.

Conveniently th compounds of formula (V) are prepared in situ from the amine (III).

In a particular aspect of tha process (B) when Y is the group $NHCOR_a$ and R_a is a 1-imidazole group, the imidazolide (V) may be formed in situ in which case the amine of formula (VI) will be mixed with the compound of formula (III)



(III)

in the presence of carbonyldiimidazole under the aforementioned conditions.

For process B when Y is the group $NHCOR_a$ and R_a is a nitro substituted phenoxy group the reaction with the primary amine (VI) is preferably carried out in the presence of a base such as a tertiary amine e.g. triethylamine.

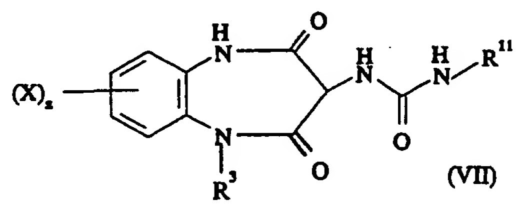
For process B when Y is the isocyanate group -N=C=O the reaction with the primary amine (VI) is preferably carried out in an aprotic solvent such as a halohydrocarbon e.g. methylene chloride. Conveniently the isocyanate is generated in situ prior to the addition of the primary amine (VI).

The compounds of formula (V) wherein R_a is an optionally substituted phenoxy group may be prepared from the primary amine (III) by reaction with the corresponding nitro substituted phenyl chloroformate in the presence of a base such as pyridine. The reaction may be carried out in a solvent such as a halohydrocabon e.g. dichloromethane and at a temperature from 0-50^0.

Compounds of formula (V) wherein R_a is a 1-imidazole group may be prepared by reacting a compound of formula (III) with carbonyldiimidazole in the presence of a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an ether (e.g. tetrahydrofuran) at a temperature ranging from 0^0 to 80^0 (conveniently at room temperature).

Compounds of formula (V) wherein Y is the isocyanate grouping -N=C=O or carbamoyl chloride -NHCOCl may be prepared from the primary amin (III) by reaction with phosgene ($COCl_2$) or triphosgene in a suitable solvent such as methylene chloride.

According to a further general process C compounds of formula (I) may also be prepared by a reaction of the compound of formula (VII)


(VII)

with an acetylbromide or chloride having the formula (VIII)

$$R^1COCH_2hal \qquad (VIII)$$

wherein hal = Cl or Br.

The reaction is conveniently carried out by treating the compound of formula (VII) with a strong base such as sodium hydride in a polar aprotic solvent such as N,N-dimethylformamide followed by reaction with the acetyl halide (VIII).

The acetyl halide (VIII) is prepared by the reaction of the amine R^1-H with corresponding haloacetyl bromide in dichloromethane at 0^oC, with a suitable base, such as triethylamine.

The amines R^1-H wherein R^1 is the group $-NR^4R^5$, may be prepared by the reductive alkylation of the amine H_2N-R^5 with an appropriate aldehyde or ketone.

According to general process D, compounds of general Formula (I) may also be prepared by the reaction of the intermediate of Formula (III) with acids of Formula (IX), as set forth below.

$$HOOC-R^2 \qquad (IX)$$

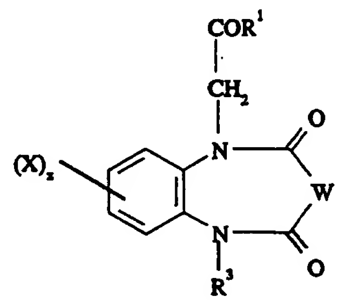
Thus reaction of the int rm diates of formula (III) with the acid of formula (IX) may be carried out in the presence of a suitable dehydrating agent such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP).

Alternatively, compounds of general Formula (I) may be obtained by reaction of the intermediates of Formula (III) with an activated derivative of the acid (IX) such as an acid chloride or anhydride thereof, including mixed anhydrides.

Preferred solvents for general process D include N,N-dimethylformamide or dichloromethane. Preferred temperatures are between 0-60^{0}C. Preferred bases for this reaction include triethylamine or N,N-dimethylaminopyride (DAMP).

According to a further general process (E) compounds of the invention may be converted into other compounds of the invention. Thus for example compounds of formula (I) wherein R^8 is the group $(CH_2)_bCO_2H$ may be preapred by reaction of a compound of formula (I) wherein R^8 is hydrogen with compound $Br(CH_2)_bCOOR^*$ wherein R^* is C_{1-4}alkyl in the presence of a strong base such as sodium hydride followed by removal of the carboxy protecting group by conventional procedures e.g. acidic or basic hydrolysis

Compounds of formula (III) may be prepared by reduction of compounds of formula (X)



(X)

wherein W is CH-N_3 or C=N-NHPh.

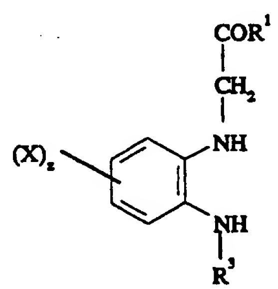
Compounds of formula (X) wherein W is CH-N_3 may be reduced to a compound of formula (III) by hydrogenation in the presence of a suitable catalyst such as 5-10% palladium on a support such as carbon or calcium

carbonate, or platinum (IV) oxide. The reaction conveniently takes place in the presence of a solvent such as an alkanol (e.g. ethanol) an ester (e.g. ethyl acetate) or acetic acid.

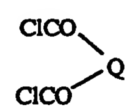
Compounds of formula (X) wherein W is C=N-NHPh may be reduced to a compound of formula (III) by reaction with zinc and acetic acid. This reaction may be carried out a temperature with the range 0-50^{0}.

Compounds of formula (X) wherein W is CHN_3 may be prepared from a compound of formula (X) wherein W is CH_2 by treatment with a strong base such as sodium hydride or potassium tert-butoxide followed by tri-isopropyl benzenesulphonyl azide or di-tertbutoxyazidodicarboxylate. The reaction conveniently takes place in a solvent such as an ether (e.g. tetrahydrofuran) at a temperature in the range of -78^{0} to 20^{0}.

Compounds of formula (X) in which W is C=NNHPh or CH_2 may be prepared by reaction of the ortho-phenylenediamine (XI) with the diacid chloride (XII) wherein Q is CH_2 or C=NNHPh, in a suitable solvent such as an ether e.g. tetrahydrofuran



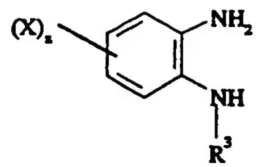
(XI)



(XII)

The compound of formula (XII) wherein Q is C = NNHPh may be prepared by reaction of ketomalonic acid with phenyl hydrazone followed by reaction with phosphorus pentachloride.

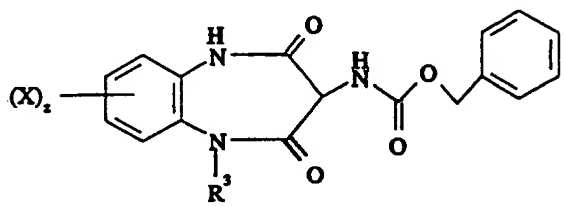
Compounds of formula (XI) are either known compounds or may be prepared by analogous methods. Thus for example a compound of formula (XI) may be prepared by alkylation of the amine (XIII).



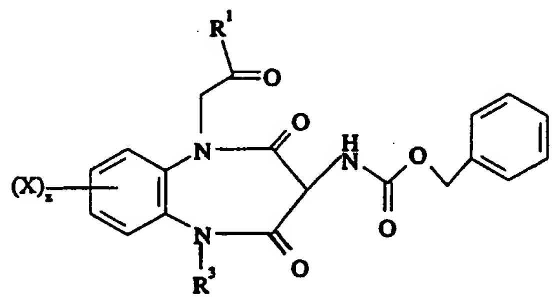
(XIII)

Thus the amine (XIII) may be reacted with the compound R_1COCH_2hal wherein hal is chlorine or bromine, optionally in the presence of sodium iodide in a solvent such as N,N-dimethylformamide.

An alternative preparation of the intermediate of Formla (III) as set forth below, involves treatment of the intermediate of Formula (XIV) with sodium hydride followed by addition of an acetyl halide (VIII) in a suitable solvent, such as N,N-dimethyl formamide, at o^0C to provide the protected intermediate of Formual (XV)



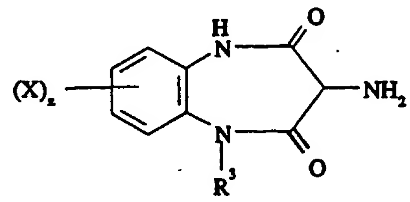
(XIV)



(XV)

Intermediate (XV) is converted to the required amine (III) by catalytic hydrogenation (40 - 60 psi) using a suitable catalyst, such as 5-10% pd/C, in a suitable solvent, such as methanol, ethanol, ethyl acetate, chloroform or acetic acid, at room temperature. Alternatively, intermediate (XVI) may be converted to amine (III) by treatment with HBr in methylene chloride.

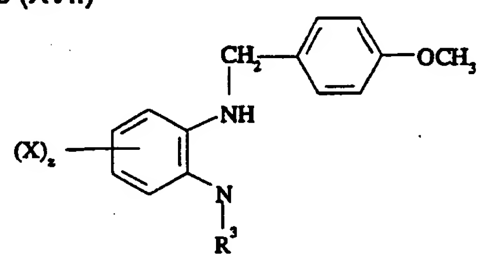
Intermediate (XIV) is obtained from the intermediat of Formula (XVI) by reaction with benzyloxychloroformate in dichloromethane, using triethylamin as base. This reaction is run conveniently at room temperature.



(XVI)

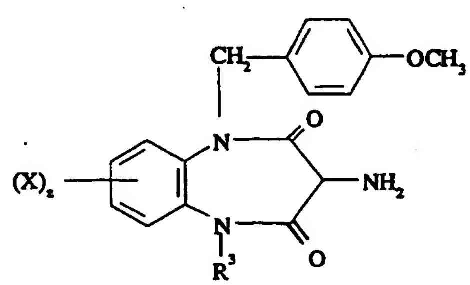
Intermediate (XVI) is prepared from phenylene diamine (XIII) by the following process.

Reaction of the diamine (XIII) with p-methyoxylbenzoylochloride followed by reduction of the amide thus formed with lithium aluminum hydride yields the N-protected diamine (XVII)



(XVII)

Reaction of compound (XVII) with the diacid chloride (XII; Q = C=NNHPh) followed by reduction with zinc and acetic acid yields the amine (XVIII)



(XVIII)

The compound of formula (XVIII) may be converted into the requir d compound (XVI) by rection with $Ce(NO_2)_6NH_4$ (ceric ammonium nitrat).

Compounds of formula (I) contain at least one asymmetric carbon atom, namely the carbon atom of the diazepine ring to which the substituted urea grouping is attached. Specific enantiomers of the compounds of formula (I) may be obtained by resolution of the racemic compound using conventional procedures such as chiral HPLC. Alternatively the required enantiomer may be prepared from the corresponding enantiomeric amine of formula (III) using any of the processes described above for preparing compounds of formula (I) from the amine (III). The enantiomers of the amine (III) may be prepared from the racemic amine (II) using conventional procedures such as salt formation with a suitably optically active acid or by preparative chiral HPLC.

EXAMPLES

The following examples are set forth to illustrate the synthesis of some particular compounds of the present invention and to further exemplify particular applications of general process A-E. Accordingly, the following Example section is in no way intended to limit the scope of the invention contemplated herein.

GENERAL PROCEDURES

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. The following solvents and reagents have been described by acronyms: tetrahydrofuran (THF), dimethylsulfoxide (DMSO), dichloromethane (DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), 1, 1-carbonyldiimidazole (CDI), isobutylchloroformate (iBuCF) N-hydroxysuccinimide (HOSu), N-hydroxybenztriazole (HOBT), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOP), tert-butyloxycarbonyl (BOC), benzyloxycarbonyl (Cbz).

The ^{1}HNMR spectra were recorded on either a Varian VXR-300 or a Varian Unity-300 instrument. Chemical shifts are expressed in parts per million (ppm, d units). Coupling constants are in units of hertz (Hz). Splitting patterns are designated as s, singlet; d, doubl t; t, tripl t; q, quart t; m, multiplet; b, broad.

Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102 or a SCIEX-APIiii spectrometers. All mass spectra were taken in the positive ion mode under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI) or by fast atom bombardment (FAB) methods. Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. Rotations were recorded on a Perkin-Elmer 241 polarimeter. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 7% ethanolic phosphomolybdic acid or p-anisldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

Products were purified by preparative reversed phase high pressure liquid chromatography (RP-HPLC) using a Waters Model 3000 Delta Prep equipped with a Delta-pak radial compression cartridge (C_{18}, 300 A, 15m, 47 mm X 300 mm). Linear gradients were used in all cases and the flow rate was 100 ml/minute (t_0 = 5.0 min.). All solvents contained 0.1% trifluoroacetic acid (TFA). Analytical purity was assessed by RP-HPLC using a Waters 600E system equipped with a Waters 990 diode array spectrometer (t range 200-400 nM). The stationary phase was a Vydac C_{18} column (5m, 4.6 mm X 250 mm). The flow rate was 1.0 to 1.5 ml/min. (t_0 = 2.8 or 3.0 min.) and the solvent systems were as described above. Data reported as tr, retention time in minutes (% acetonitrile over time).

Using the general processes A-E outlined above, the following compounds of the invention have been made.

Example 1

2-[2, 4-Dioxo-5-phenyl-3-(3-phenyl-ureido)-2, 3, 4, 5-tetrahydro-benzo[b] [1, 4] diazepin-1-yl]-N-isopropyl-N-phenyl-acetamide

To a solution of 1-(2, 4-dioxo-1-phenyl-2, 3, 4, 5-tetrahydro-1H-benzo [b] [1, 4]-diazepin-3-yl)-3-phenyl urea (0.100 g.) in N,N-dimethylformamide (2 ml) cooled to 3°C, was added sodium hydride (0.0104 g; 60% suspension in mineral oil) with stirring. The mixture was stirred 20 minut s, th n 2-bromo-N-isopropyl-N-phenyl acetamide (0.0656 g) was added in on portion. The resultant mixture was stirred at ambient temperature ov might. The crude

reaction mixture was purified by preparative RP-HPLC with a gradient lution of 60-72% acetonitrile in water with 0.1% trifluoroacetic acid buffer ov r a 30 minut period at a rat of 100 ml/min. Fractions containing the desired material were combined, frozen and lyophilized to provide the title compound (0.0653 g) as a white powder. ^1H NMR (300MHz, DMSO-d_6): d 0.95 (d, J= 7.3Hz, 3H), 0.98 (d, J= 7.3Hz, 3H), 4.19 (d, J= 16.6Hz, 1H), 4.48 (d, J= 16.9Hz, 1H), 4.79 (m, 1H), 5.04 (d, J= 7.8Hz, 1H), 6.87-6.92(m, 1H), 6.95(d, J= 7.6Hz, 1H), 7.18-7.57 (m, 17H), 9.14 (s, 1H); MS (FAB): m/z= 562 (MH^+);TLC (CH_2Cl_2/CH_3OH, 19:1): R_f= 0.19; RP-HPLC (Vydac C-18, 25cm x 4.6mm; 60-72% CH_3CN in H_2O with 0.1% TFA buffer; 30 minutes; 1 ml/min): t_r= 17.5min (t_o= 2.5min); m.p.: 230-235°C

Enantiomers of the title compound (0.014 g) were separated on a Pirkle covalent (L)-Phenylglycine column, 25cm x 10.0mm, with an isocratic eluant of methanol/water (80:20) at a rate of 5 ml/min. Fractions from the four injections corresponding to the first eluted enantiopode were combined and evaporated under reduced pressure to give enantiomer 1 as a white powder. Likewise, fractions corresponding to the second eluted enantiopode were combined and evaporated under reduced pressure to give entantiomer 2 as a white powder.

Enantiomer 1: Chiral HPLC (Pirkle covalent (L)-Phenylglycine, 25cm x 4.6mm; CH_3OH/H_2O (78:22) isocratic; 1.5 ml/min): t_r= 14.5min (t_o= 2min); MS (FAB): m/z= 562.1 (MH^+)

Enantiomer 2: Chiral HPLC (Pirkle covalent (L)-Phenylglycine, 25cm x 4.6mm; CH_3OH/H_2O (78:22) isocratic; 1.5 ml/min): t_r= 18min (t_o= 2min); MS (FAB): m/z= 562.0 (MH^+)

Example 2

1H-Indole-2-carboxylic acid [1-(Isopropyl-phenyl-carbamoylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-amide

To a vigorously stirred solution of 2-(3-Amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-benzo [b] [1, 4] diazepine-1-yl)-N-isopropyl-N-phenyl acetamide (0.116 g) in N,N-dimethylformamide (5 ml) at ambient temperature was added indole-2-carboxylic acid (0.0423 g, 0.262 mmol), N-hydroxybenzotriazole (0.0354 g), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0503 g) successiv ly. Tri thylamin (8

drops) was added dropwise to maintain the basicity (pH = 9) of the solution was reached. The resultant mixtur was stirred at ambi nt temperature for five hours. The solvent was evaporated in vacuo to give a yellow oil which was purified by flash chromatography on silica gel (9 g) with an eluant of a mixture of ethyl acetate and hexane (2:3, 200 ml). Fractions containing the desired product were combined and evaporated in vacuo to give the title compound (0.141 g) as a white foam. ^{1}H NMR (300MHz, $CDCl_3$): d 1.06 (d, J= 7.3Hz, 3H), 1.09 (d, J= 7.3Hz, 3H), 4.22 (d, J= 16.6Hz, 1H), 4.40(d, J= 16.4Hz, 1H), 5.02(m, 1H), 5.50(d, J= 7.1Hz, 1H), 7.02(d, J= 8.1Hz, 1H), 7.10-7.47 (m, 16H), 7.57 (d, J= 6.8Hz, 1H), 7.67 (d, J= 7.8Hz, 1H), 9.29 (br s, 1H); MS (FAB): m/z= 586.0 (MH^+); TLC (EtOAc/Hexane (2:3)): R_f= 0.16; RP-HPLC (Vydac C-18, 25cm x 4.6mm; 51-60% CH_3CN in H_2O with 0.1% TFA buffer; 30 minutes; 1 ml/min): t_r= 19.5min (t_0= 3min)

Example 3

1H-Indole-2-carboxylic acid {1-[Isopropyl-(4-methoxyphenyl)carbamoyl-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl}-amide

To a solution of 2-(3-Amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-benzo [b] [1, 4] diazepine-1-yl)-N-isopropyl-N-(4-methoxy-phenyl)-acetamide (500mg) in N,N-dimethylformamide (15mL) were added indole-2-carboxylic acid (174mg), N-hydroxybenzotriazole (143mg), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (.203g) successively with stirring at ambient temperature. The resultant mixture was stirred at ambient temperature for 18 hours. The solvent was evaporated under reduced pressure to give a yellow oil which was taken into ethyl acetate(75mL), washed with water (2 x 30mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to a give a tan foam. The crude product was purified via preparative HPLC chromatography on a Delta-Pak C-18 column eluted with a linear gradient from 50% to 60% acetonitrile in water with 0.1% trifluoroacetic acid buffer over a 30 minute period at a rate of 100mL/min. Appropriate fractions were combined, frozen and lyophilized to give the TFA salt of the title compound (.550g) as a white powder.

^{1}H NMR (300MHz, $CDCl_3$): d 1.06(m, 6H), 3.85(s, 3H), 4.27(d, J= 16.6Hz, 1H), 4.34(d, J= 16.6Hz, 1H), 4.99(m, 1H), 5.51(d, J= 7.4Hz, 1H), 6.96-7.42(m, 17H), 7.66(m, 2H), 9.54(br s, 1H)

TLC (dichloromethane/methanol(9:1)): R_f= 0.64

MS (FAB): m/z= 616.2 (MH^+) (calcd. for $C_{36}H_{33}N_5O_5$= 615.2484)

Example 4

2-[1-(Isopropyl-phenyl-carbamoylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-ylcarbamoyl]-indol-1-yl-acetic acid.

To a vigorously stirred solution of 1H-indole-2-carboxylic acid [1-(Isopropyl-phenyl-carbamoylmethyl)-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1H-benzo[b][1, 4]diazepin-3-yl]-amide (0.101 g) in N,N-dimethylformamide (3 ml) cooled to 3°C was added sodium hydride (0.0083 g) (60% suspension in mineral oil). After 20 minutes, t-butylbromoacetate (0.0336 g) was added. The resultant mixture was stirred with cooling in an ice bath for 90 minutes followed by slow warming to ambient temperature and stirring overnight. The solvent was evaporated under reduced pressure to give a brown oil which was dissolved in dichloromethane (30 ml) and washed successively with saturated aqueous sodium bicarbonate (20 ml) and brine (20 ml). The resultant solution was dried over sodium sulfate, filtered and evaporated under reduced pressure to give a yellow oil (0.142 g) which was purified by flash chromatography on silica gel (9 g) with an eluant of a mixture of ethyl acetate and hexane (1:2, 200 ml). Fractions containing the desired product were combined and evaporated to give 2-{1-(Isopropyl-phenyl-carbamoylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-ylcarbamoyl]-indol-1-yl}-acetic acid tert-butyl ester (.092 g) as a white foam. ^1H NMR (300MHz, $CDCl_3$): d 1.07 (d, J= 4.9Hz, 3H), 1.09 (d, J= 4.6Hz, 3H), 1.37 (s, 9H), 4.17 (d, J= 16.6Hz, 1H), 4.44 (d, J= 16.9Hz, 1H), 5.01 (m, 1H), 5.18 (d, J= 17.1Hz, 1H), 5.24 (d, J= 18Hz, 1H), 5.47 (d, J= 7.6Hz, 1H), 7.01 (dd, J= 1.2, 8.3Hz, 1H), 7.13-7.51 (m, 17H), 7.57 (d, J= 7.3Hz, 1H), 7.67 (d, J= 7.8Hz, 1H); MS (FAB): m/z= 700.2 (MH^+); TLC (EtOAc/Hexane, 2:3): R_f= 0.35; RP-HPLC (Vydac C-18, 25cm x 4.6mm; 60-70% CH_3CN in H_2O with 0.1% TFA buffer; 30 minutes; 1 ml/min): t_r= 17.5min (t_0= 3min)

To a solution of {2-[1-(Isopropyl-phenyl-carbamoylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-ylcarbamoyl]-indol-1-yl}-acetic acid tert-butyl ester (0.072 g) in dichloromethane (4 ml) at ambient temperature was added trifluoroacetic acid (1.5 ml) gradually with stirring. After the reaction was stirred 30 minutes, th dichloromethan and trifluoroacetic acid wer evaporated under reduced pressure to afford a cl ar

glass. The glass was purified by preparative RP-HPLC on a C-18 column with a gradient elution of 45-55% acetonitrile in water with 0.1% trifluoroacetic acid buffer ov r a 30 minut period at a rate of 100 ml/min. Fractions containing the desired material were combined, frozen and lyophilized to afford the title compound (0.050 g) as a white powder. ^1H NMR (300MHz, $CDCl_3$): d 1.07 (d, J= 4.4Hz, 3H), 1.10 (d, J= 4.4Hz, 3H), 4.23 (d, J= 16.6Hz, 1H), 4.40 (d, J= 16.6Hz, 1H), 5.01 (m, 1H), 5.06 (s, 2H), 5.44 (d, J= 7.1Hz, 1H), 7.03 (dd, J= 1.2, 8.1Hz, 1H), 7.17-7.52 (m, 17H), 7.67 (d, J= 8.1Hz, 1H), 7.74 (d, J= 7.1Hz, 1H); MS (ES): m/z= 644.2 (MH^+); TLC (CH_2Cl_2/CH_3OH(19:1)): R_f= 0.15; RP-HPLC (Vydac C-18, 25cm x 4.6mm; 45-55% CH_3CN in H_2O with 0.1% TFA buffer; 30 minutes; 1 ml/min): t_r= 22min (t_o= 3min).

Example 5

2-(2,4-dioxo-5-phenyl-3-{3-[3-(1H-tetrazol-5-yl)-phenyl]-ureido} 2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl) N-isopropyl-N-phenylacetamide

To a vigorously stirring solution of 2-(3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)-N-isopropyl-N-phenyl-acetamide (.070 g) in tetrahydrofuran (3 ml) at ambient temperature was added 1,1-carbonyldiimidazole (.025 g) in one portion. The resulting mixture was stirred for 90 minutes at ambient temperature. 3-(2H-tetrazol-5-yl)-phenylamine hydrochloride (31.3 mg), was added in one portion and the reaction mixture was heated to reflux overnight. The reaction mixture was filtered and the filtrate concentrated to a yellow oil. The oil was purified by preparative RP-HPLC on a C-18 column with a gradient elution of 43-53% acetonitrile in water with 0.1% trifluoroacetic acid buffer over a 30 minute period at a rate of 100 ml/min. Fractions containing the desired material were combined, frozen and lyophilized to provide the title compound as a white powder (50 mg).

^1H NMR (300MHz, DMSO-d_6): d 0.96(d, J= 7.3Hz, 3H), 0.98(d, J= 7.3Hz, 3H), 4.20(d, J= 16.8Hz, 1H), 4.49(d, J= 17.1Hz, 1H), 4.79(m, 1H), 5.06(d, J= 7.3Hz, 1H), 6.98(m, 2H), 7.24-7.55(m, 17H), 8.17(s, 1H), 9.44(s, 1H)

MS (FAB): m/z= 630.2 (MH^+) (calcd. for $C_{34}H_{31}N_9O_4$= 629.2502)

TLC (CH_2Cl_2/CH_3OH(9:1)): R_f= 0.24

RP-HPLC (Vydac C-18, 25cm x 4.6mm; 43-53% CH_3CN in H_2O with 0.1% TFA buffer; 30 minutes; 1 ml/min): t_r= 15min (t_o= 3min)

Example 6

3-{3-[1-(Isopropyl-phenyl-carbamoylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-3-yl]-ureido} benzoic acid ethyl ester

A solution of 3-ethoxycarbonyl phenylisocyanate (124 mg) in dichloromethane (3 ml) was added to a solution of 2-(3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl-N-isopropyl-N-phenylacetamide (288 mg), in dichloromethane (3 ml). The reaction was allowed to stir at room temperature for 30 minutes. The dichloromethane was evaporated *in vacuo* and the residue was suspended in acetonitrile and heated at reflux for 1 hour with stirring. Compound 40 precipitated upon cooling to 0^oC. The filtrate was washed with cold acetonitrile to give the title compound as a white solid (312 mg, 76%). ^1H-NMR (300 MHz, d_6-DMSO): d 9.4 (s, 1H), 8.05 (s, 1H), 7.6 - 6.9 (m, 18H), 5.05 (d, 9 Hz, 1H), 4.8 (m, 1H), 4.48 (d, 16 Hz, 1H), 4.3 (dd, 6.8 Hz, 2H), 4.18 (d, 15.8 Hz, 1H), 1.27 (t, 7.2 Hz, 3H), 0.96 (m, 6H); MS (FAB) = 634 (MH^+).

Example 7

3-{3-[1-(Isopropyl-phenyl-carbamoylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-3-yl]-ureido} benzoic acid

A solution of 3-{3-[1-(Isopropyl-phenyl-carbamoylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-3-yl]-ureido} benzoic acid ethyl (312 mg, 0.493 mol) in methanol (23 ml) and tetrahydrofuran (10 ml) was heated to reflux. Aqueous 5% potassium carbonate (6.5 ml) is added and the reflux was maintained for 2.5 hours. The reaction mixture was concentrated *in vacuo* and the residue was neutralized and triturated with 1N HCl and water to give the crude product. The crude product was dissolved in ethyl acetate (20 ml), heated to reflux for 3 hours then cooled. The resulting precipitate was separated by filtration and dried under vacuum to provide the title compound as a white solid (225 mg, 75%). ^1H-NMR (300 MHz, d_6-DMSO): d 9.4 (s, 1H), 8.05 (s, 1H), 7.6 - 6.9 (m, 18H), 5.05 (d, 9 Hz, 1H), 4.8 (m, 1H), 4.48 (d, 16 Hz, 1H), 4.18 (d, 15.8 Hz, 1H), 0.96 (m, 6H); MS (FAB) = 606 (MH^+).

The aforementioned Examples are set forth so as to better illustrate synthesis approaches for preparing the compounds of th pres nt invention. Additionally, particular intermediates useful in the general processes set forth herein can be prepared as set forth below.

Intermediate 1

2-(phenylhydrazono)-malonic acid

To a vigorously stirred solution of ketomalonic acid monohydrate (29.33 g) in ethanol (140 ml) and water (300 ml) at ambient temperature was added phenylhydrazine (23.3 g) dropwise over a 40 minute period. The resultant slurry was stirred overnight at ambient temperature. The solid was separated by filtration, washed sucessively with cold water (100 ml) and ethanol (25 ml) and air dried. Subsequent drying was performed at 75°C overnight in a vacuum oven to give the title compound as a yellow solid (42.38 g). ^{1}H (300MHz, DMSO-d_6): d 7.12(t, 1H), 7.35-7.48(m, 4H); m.p.: 155-157°C (dec).

Intermediate 2

2-(phenylhydrazono)-propanedioyl dichloride

To a stirred slurry of Intermediate 1 (14.73 g), in chloroform (90mL) at 5°C was added phosphorous pentachloride (36.84 g) portionwise over a 20 minute period. After complete addition, the solution was warmed to room temperature and stirred one hour followed by heating to reflux for three hours. The solution was cooled in an ice bath and the resultant precipitate was separated by filtration, washed with cold hexane (50 ml), and dried under vacuum overnight to give the title compound (13.4 g) as a bright yellow solid. ^{1}H (300MHz, DMSO-d_6): d 7.12(t, 1H), 7.20-7.56(m, 4H); m.p.: 135-138°C (dec).

Intermediate 3

4-methoxy-N-(2-phenylaminophenyl)benzamide

A vigorously stirring solution of N-phenyl-1,2-phenylenediamine (20.15g) in dichloromethane (325 ml) and triethylamine (11.07 g) was cooled in an ice/aceton bath under nitrogen. p-Anisoyl chloride (18.66 g) dissolv d in dichloromethane (100 ml) was added dropwise over a 20 minut period while

maintaining a t mperature of <5°C. The r action mixture was allowed to warm to ambient temperature and stirred for two hours. The organic solution was washed successively with water (200 ml), 2N aqueous HCl (80 ml), and saturated brine solution (160 ml), then dried over sodium sulfate and passed through a pad of silica (150 g). The silica was eluted with ethyl acetate (1L) and the eluent was evaporated in vacuo to a pink solid. The solid was triturated overnight with ethyl ether (350 ml), cooled in an ice bath, filtered, and dried in vacuo to give the title compound as a light pink solid (21.67 g). ^1H (300MHz, $CDCl_3$): d 3.82 (s, 3H), 5.75 (br s, 1H), 6.80-6.91(m, 5H), 7.12-7.29 (m, 5H), 7.62 (d, J= 8.8Hz, 2H), 8.15 (dd, J= 1.7, 7.8Hz, 1H), 8.36 (s, 1H); TLC (EtOAc/Hex, 1:4): R_f= 0.24; m.p.: 148-150°C

Intermediate 4

N-(4-Methoxybenzyl)-N'-phenyl-benzene-1, 2-diamine.

To a stirred solution of lithium aluminum hydride (1.0 g) in THF (40 ml) cooled to 5°C was added a solution of 4-methoxy-N-(2-phenylamino-phenyl)-benzamide (5.0 g) in THF (30 ml) over a 45 minute period. After complete addition, the reaction mixture was heated to reflux for 1.5 hrs. The solution was cooled to room temperature and excess lithium aluminum hydride was quenched with ethanol until hydrogen evolution ceased. Saturated agueous sodium hydrogen carbonate (100 ml) was added and the resultant solution extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried with sodium sulfate and filtered through a pad of silica. The silica pad was washed with ethyl acetate (500 ml) and the organic fractions were combined. The filtrate was concentrated in vacuo to a brown oil which solidified on standing to give the title compound . (4.78 g). ^1H (300MHz, $CDCl_3$): d 3.79 (s, 3H), 4.27 (s, 2H), 4.52 (br s, 1H), 5.08 (s, 1H), 6.67-6.74 (m,4H), 6.79-6.86 (m, 3H), 7.04-7.24 (m, 6H); TLC (EtOAc/Hex (1:4)): R_f= 0.57

Intermediate 5

1-(4-Methoxybenzyl)-5-phenyl-3-(phenylhydrazono)-
1, 5-dihydro-benzo [b] [1, 4] diazepine-2, 4-dione

Solutions of Intermediate 4 (4.86 g) in THF (40 ml) and 2-(phenylhydrazono) propandioyl dichloride (5.58 g) in THF (40 ml) were add d concomitantly dropwise with stirring in an ice/m thanol bath over a 30 minute p riod. The

solution was allowed to warm to room temperature and stirred ov might. A yellow pr cipitate was separated by filtration, washed with cold THF (40 ml), air dried and dried in vacuo overnight to give the title compound (6.23 g) as a yellow solid. ^{1}H (300MHz, $CDCl_3$): d 3.78 (s, 3H), 4.69 (d, J= 14.7Hz, 1H), 5.76 (d, J= 14.9Hz, 1H), 6.80-6.87 (m, 3H), 7.02-7.12 (m, 4H), 7.19-7.40 (m, 11H), 11.19 (s, 1H); MS (FAB): m/z= 477.0 (MH^+); TLC (EtOAc/Hex, 1:4): R_f= 0.18

Intermediate 6

3-Amino-1-(4-methoxybenzyl)-5-phenyl-1,5-dihydrobenzo[b][1, 4] diazepine-2,4-dione

To a vigorously stirred slurry of zinc dust (6.49 g) in acetic acid (50 ml) cooled to 10°C, was added a slurry of 1-(4-Methoxybenzyl)-5-phenyl-3-(phenylhydrazono)-1, 5-dihydrobenzo [b] [1, 4] diazepine-2, 4-dione (5.75 g,12.1 mmol) in acetic acid (30 ml) over a fifteen minute period. After complete addition, the solution was warmed to room temperature and stirred three hours. The zinc was separated by filtration and washed with ethyl acetate (75 ml). The filtrate was concentrated in vacuo and partitioned between H_2O (60 ml) and ethyl acetate (100 ml). The pH was adjusted to 9 with saturated aqueous sodium carbonate and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 75 ml), the organic layers combined, dried with magnesium sulfate, filtered and concentrated in vacuo to give a yellow oil which was dried in vacuo to give the title compound (4.79 g) NMR (300 MHz, $CDCl_3$): d 3.05 (s, 2H), 3.75 (s, 3H), 4.35 (s, 1H), 4.64 (d, J= 14.7Hz, 1H), 5.82 (d, J= 14.7Hz, 1H), 6.59-6.85 (m, 6H), 7.06-7.29 (m, 6H), 7.51(d, J= 7.4Hz, 1H); MS (FAB): m/z= 388.2 (MH^+); TLC (CH_2Cl_2/CH_3OH (9:1)): R_f= 0.50

Intermediate 7

3-Amino-1-phenyl-1,5-dihydrobenzo[b][1,4] diazepine-2, 4-dione

To a stirred solution of 3-amino-1-(4-methoxybenzyl)-5-phenyl-1,5-dihydrobenzo [b] [1, 4] diazepine-2,4-dione (0.50 g) in acetonitrile/H_2O (9:1, 12 ml) at ambient temperature was added cerric ammonium nitrate (1.84 g) portionwise over a ten minute period. The solution was stirred overnight at room temperature. The solution was concentrated in vacuo and the resultant solid partitioned between saturated aqueous potassium carbonate (40 ml) and ethanol (60 ml). The phas s were separat d and th aqueous phas

extract d with thanol (4 x 50 ml). The ethanol portions were combined, dried over sodium sulfate and concentrated in vacuo to a tan solid. This solid was extracted exhaustively with boiling CH_2Cl_2 (10 x 60 ml), the organics combined, dried over sodium sulfate, filtered and concentrated to give the title compound (0.30 g) as a tan solid. ^1H (300MHz, DMSO-d_6): d 1.98 (br s, 2H), 4.08 (s, 1H), 6.86 (d, J= 8.4Hz, 1H), 7.11-7.46 (m, 8H), 10.78 (br s, 1H); ^{13}C (75.429MHz, DMSO-d_6): d 56.98, 123.41, 126.22, 126.51, 127.34, 128.30, 128.89, 130.15, 132.29, 134.42, 142.36, 168.13, 169.39. MS (FAB): m/z= 268.10 (MH^+); TLC (CH_2Cl_2/CH_3OH,15:1): R_f= 0.21

Intermediate 8

1-(2, 4-Dioxo-1-phenyl-2, 3, 4, 5-tetrahydro-1H-benzo [b] [1, 4]-diazepin-3-yl)-3-phenyl urea

To a slurry of 3-amino-1-phenyl-1, 5-dihydro-benzo [b] [1,4]-diazepine-2, 4-dione (0.398 g) in dichloromethane (5 ml) was added phenyl isocyanate (0.177 g) gradually with stirring at ambient temperature. The reaction mixture was stirred two hours at ambient temperature after which time a cream precipitate was separated by filtration to provide the title compound (0.413 g). ^1H NMR (300MHz, DMSO-d_6): d 4.97 (d, J= 7.5 Hz, 1H), 6.88-6.97 (m, 3H), 7.13-7.47 (m, 12H), 9.16 (s, 1H), 10.78 (br s, 1H); TLC (CH_2Cl_2/CH_3OH,19:1): R_f= 0.21

Intermediate 9

N-isopropyl-N-phenyl-2-(2-phenylaminophenylamino)-acetamide

Potassium carbonate (6.9 g) was added to a solution of N-phenylphenylene diamine (9.2 g) in DMF and 2-bromo-N-isopropyl-N-phenyl acetamide (12.7 g) in DMF (200 ml) and the mixture was allowed to stir overnight. The DMF was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (400 ml) and washed exhaustively with aqueous 1N HCl (4 x 250 ml). The organic layer was washed with water (2 x 200 ml), dried (Na2SO4) and evaporated to give 17.8 gm of crude alkylated product. The oil was purified by chromatography on silica gel (600 g) using first $CHCl_3$ (8000mL), then hexane:ethyl acetate (2:1, 8000 ml) as eluents to give the title compound (10 g), as an oil. ^1H-NMR (300 MHz, $CDCl_3$): d 7.42 - 6.8 (m, 14 H), 6.36 (d, 1H), 4.95 (m, 1H), 3.22 (s, 2H), 1.05 (d, 6H); MS (FAB) = 360 (MH^+) ; TLC, Rf = 0.18 ($CHCl_3$).

Intermediate 10

2-[2,4-dioxo-5-phenyl-3-(phenylhydrazono)-2,3,4,5-tetrahydro benzo[b][1,4]diazepin-1-yl]-N-isopropyl-N-phenylacetamide

N-isopropyl-N-phenyl-2-(2-phenylaminophenylamino)-acetamide (10 g) and 2-(phenyl-hydrazono)-propanedioyl dichloride (6.83 g), were each dissolved in THF (100 ml) and added simultaneously, with stirring, to a flask containing THF (100 ml) at 0^{o}C, under nitrogen. The reaction mixture was allowed to warm to R.T. and stirred four hours. The THF was evaporated in vacuo and the residue was dissolved in ethyl acetate (200 ml). The ethyl acetate solution was washed with 10% aqueous sodium carbonate (2 x 200 ml) and water (2 x 200 ml), dried (Na_2SO_4), and concentrated in vacuo. The residual foam was treated with diethyl ether (50 ml) to precipitate the title compound as a bright yellow solid (7.5 g). The mother liquor was concentrated to a tan foam (2.5 g). ^{1}H-NMR (300 MHz, $CDCl_3$): d 11.4 and 10.85 (s, 1H), 7.6 - 6.8 (m, 19 H), 5.05 (m, 1H), 4.4 (m, 2H), 1.05 (m, 6H); MS (FAB) = 532 (MH$^+$) ; TLC, Rf = 0.19 (hexane:ethyl acetate, 2:1).

Intermediate 11

2-(3-Amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo-[b][1,4]diazepin-1-yl)-N-isopropyl-N-phenylacetamide

Zinc powder (9.1 g) was added in portions to a slurry of 2-[2,4-dioxo-5-phenyl-3-(phenylhydrazono)-2,3,4,5-tetrahydro benzo[b][1,4]-diazepin-1-yl]-N-isopropyl-N-phenylacetamide (7.5 g), in glacial acetic acid, cooled to 0^{o}C. The reaction was allowed to warm to R.T. and stirred an additional hour. The zinc was filtered through a celite pad and the glacial acetic acid was evaporated in vacuo. The residue was dissolved in ethyl acetate (200 ml) and washed with 10% aqueous sodium carbonate (2 x 100 ml) and water (2 x 100 ml), dried (Na_2SO_4) and evaporated to a tan oil. Trituration with hexane and ethyl acetate provided the title compound as a light tan powder (6.3 g). ^{1}H-NMR (300 MHz, $CDCl_3$): d 7.6 - 6.8 (m, 14H), 5.05 (m, 1H), 4.3 - 4.0 (m, 3H) 1.05 (d, 6H); MS (FAB) = 448 (MH$^+$) ; TLC, Rf = 0.25 (chloroform:methanol, 9:1).

Intermediate 12

2-(3-Amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-benzo [b] [1, 4] diazepine-1-yl)-N-isopropyl-N-(4-methoxy-phenyl)-acetamide

To a stirred solution of 2-[2,4-dioxo-5-phenyl-3-(phenyl-hydrazono)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-yl]-N-isopropyl-N-(4-methoxy-phenyl)-acetamide (4.28g) in acetic acid (50mL) at ambient temperature, was added zinc dust (4.11g) and stirred three hours. The zinc was filtered off, the filtrate concentrated in vacuo, and the resultant oil partitioned between water (60mL) and ethyl acetate (100mL). The pH was adjusted to 8 with 6N sodium hydroxide and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 75mL) and the organics combined, dried with magnesium sulfate, filtered and concentrated in vacuo to give a yellow foam. The crude product was purified via flash chromatography on silica gel (80g) eluted successively with ethyl acetate (260mL) (to remove impurity) and methylene chloride/methanol (19:1, 200ml) (to elute product). Appropriate fractions were combined and concentrated to give the title compound (2.58g) as a yellow foam.

^{1}H (300MHz, $CDCl_3$): d 1.08 (d, J=6.6Hz, 6h), 2.22 (br s, 2H), 3.85 (s, 3H), 4.12-4.35 (m, 3H), 5.01 (m, 1H), 6.91-7.00 (m, 3H), 7.12 (m, 2H), 7.22-7.43 (m, 8H)

TLC (CH_2Cl_2/CH_3OH (19:1)): R_f= 0.25

Intermediate 13

<u>2-[2,4-dioxo-5-phenyl-3-(phenyl-hydrazono)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-yl]-N-isopropyl-N-(4-methoxy-phenyl)-acetamide</u>

Solutions of N-isopropyl-N-(4-methoxy-phenyl)-2-(2-phenylamino-phenylamino)-acetamide(3.00g) in THF (30mL) and 2-(phenyl-hydrazono) propandioyl dichloride (1.89g) in THF (30mL) were added concomitantly dropwise with stirring in an ice/methanol bath over a 30 minute period. After complete addition, the solution was allowed to warm to room temperature and stirred over night. The solvent was evaporated under reduced pressure and the resultant oil taken into ethyl acetate (250mL), washed with saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (4.28g) as a yellow foam.

^{1}H (300MHz, $CDCl_3$): d 1.13 (m, 6H), 3.87 (s, 3H), 4.17-4.55 (m, 2H), 5.05 (m, 1H), 6.88-7.60 (m,18H), 10.68 (s, 0.5H), 11.44 (s, 0.5H)

TLC (EtOAc/Hex (2:3)): R_f= 0.38

Intermediate 14

N-Isopropyl-N-(4-methoxy-phenyl)-2-(2-phenylamino-phenylamino)-acetamide

To a solution of N-phenyl-benzene-1, 2-diamine(3.08g) in DMF (35mL) was added potassium carbonate (2.31g) and 2-bromo-N-isopropyl-N-(4-methoxy-phenyl)-acetamide (4.79g) and stirred 18h at ambient temperature. The solvent was evaporated in vacuo and the resultant oil was dissolved in ethyl acetate(250mL), washed with 1N HCl (4 x 100mL), dried over sodium sulfate, filtered, and concentrated to a brown oil. The oil was subjected to flash chromatogaraphy on silica gel (70g) eluted with ethyl acetate/hexanes (1:4, 1L). Fractions containing the desired product were combined and concentrated under reduced pressure to give the title compound as a tan foam (3.95g).

^{1}H NMR (300MHz, $CDCl_3$): d 1.05 (d, J=6.9Hz, 6H), 3.44 (s, 2H), 3.87 (s, 3H), 4.97 (m, 1H), 5.37 (br s, 1H) 6.36 (d, J=7.4Hz, 1H), 6.69 (t, 1H), 6.71-7.21 (m, 11H)

TLC (EtOAc/Hexane (1:4)): R_f= 0.18

Intermediate 15

2-Bromo-N-isopropyl-N-(4-methoxy-phenyl)-acetamide

To a solution of isopropyl-(4-methoxy-phenyl)-amine (25.11g) in dichloromethane (250mL) was added triethylamine (15.38g) with stirring at ambient temperature. The solution was cooled in an ice bath (<3°C) and bromoacetyl bromide (30.68g) dissolved in dichloromethane (100mL) was added dropwise over a 45 minute period with stirring and cooling in an ice bath. The reaction mix was stirred overnight at ambient temperature, washed with 0.3N HCl (300mL) and brine (300mL), dried over sodium sulfate, filtered, and evaporated under reduced pressure to give a dark brown oil. The oil was filtered through a pad of silica gel (150g) which was eluted with ethyl acetate/hexane (1:1, 900mL) and the filtrate evaporated under reduced pressure to afford the title compound (41.05g) as a brown oil which crystallized on standing.

^{1}H NMR (300MHz, $CDCl_3$): d 1.04(d, J= 6.8Hz, 6H), 3.53(s, 2H), 3.84(s, 3H), 4.93(m, 1H), 6.93(d, J= 9.1Hz, 2H), 7.10(d, J= 9.1Hz, 3H)

TLC (EtOAc/Hexane(3:17)): R_f= 0.18

Int rmediate 16

Isopropyl-(4-methoxy-phenyl)-amine

To a stirr d solution of 4-methoxy-phenylamine (1.24g) in m thanol (15mL) at ambient temperature was added successively, glacial acetic acid (415mg), acetone (669mg), and 1M sodium cyanoborohydride in THF (12.7mL). The reaction mixture was stirred overnight at room temperature. The pH was adjusted to 2 with 6N HCl and stirred for 30 minutes after which time the excess sodium cyanoborohydride was completely quenched. The pH was then adjusted to 8.5 with 1N NaOH and the resultant solution extracted with diethyl ether (2 x 50mL) and ethyl acetate (50mL). The oganic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (1.42g) as a yellow oil.

^{1}H NMR (300MHz, $CDCl_3$): d 1.18(d, J= 6.1Hz, 6H), 2.92(br s, 1H), 3.55(m, 1H), 3.75(s, 3H), 6.57(d, J= 9.1Hz, 2H), 6.78(d, J= 8.8Hz, 2H)

TLC (EtOAc/Hex (2:3)): R_f= 0.72

Intermediate 17

3-Aminobenzeneacetonitrile

A solution of 3-nitrobenzeneacetonitril (8.0g) in EtOH (100ml) was hydrogenated at 1 atm and room temperature over 5% palladium on carbon (0.8g) for 4hrs. The catalyst was removed by filtration through Hyflo and the filtrate was evaporated. The residue was chromatographed, eluting with EA:Hexane (1:2) to give the title compound (5.25g) as an orange oil.

T.l.c. hexane:EA (2:1) Rf 0.45; NMR (300 MHz, $CDCl_3$) d 3.792H,s); 3.9(2H,br); 6.7(3H,m); 7.2(H,M).

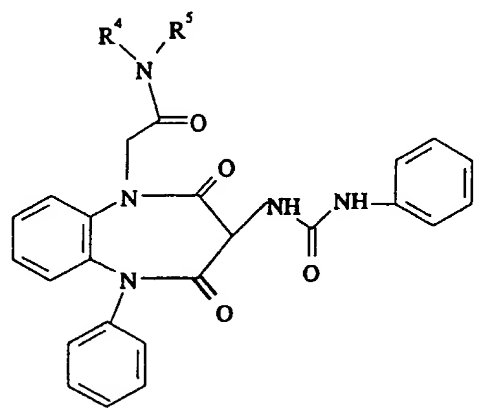
Intermediate 18

3-(2H-Tetrazol-5-yl)-phenylamine hydrochloride

3-Aminobenzonitrile (10.0 g) and tributyltinazide (42 g) were heated together at 160°C under nitrogen for 120 minutes. The cooled mixture was diluted with ether (300 ml), extracted with 2N aqueous HCl (2 x 200 ml) and the combined aqueous extracts cooled in an ice-methanol bath for 30 minutes. The resulting precipitate was separated by filtration washed with ether (100 ml) and dried to give a pale pink solid. This was recrystalized from methanol (600 ml) to give the title compound as an off-white solid (12.1 g). ^{1}H NMR

(300MHz, DMSO-d_6): d 7.32(d, J= 7.8Hz, 1H), 7.57(t, 1H), 7.82(m, 2H) m.p.: 256-262°C (dec).

Using the general processes A-E outlined above, the following compounds of the invention have also been made and are set forth below in Tables 1-9 for convenience as well as the synthesis routes for preparing them. Embodiments (A)-(H) have been provided to correlate with Tables 1-9, respectively, for convenience in illustration and for ease in identification of compounds. Groups R^{13-21} have been provided in the Tables 1-9 merely for convenience in illustration and for ease in identification of compounds.

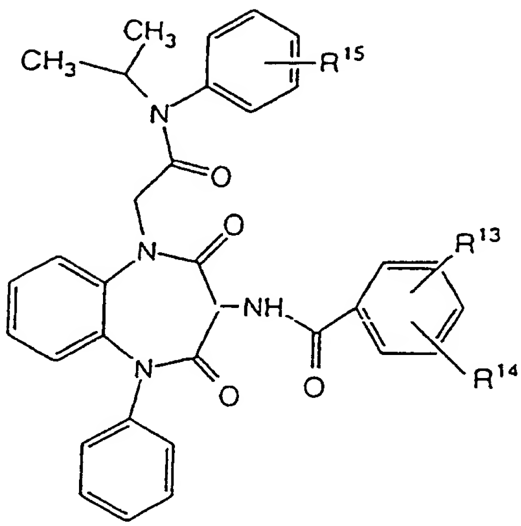


(A)

Table 1 (A)

Compound	R^4	R^5	General Process
1	CH_3	2-Cl-C_6H_4-	C
2	CH_3	2-CH_3-C_6H_4-	C
3	CH_3	2-$COOCH_3C_6H_4$-	C
4	CH_3	4-$OCH_3C_6H_4$-	C
5	CH_3	4-$COOCH_3C_6H_4$-	C
6	$(CH_3)_2CH$-	C_6H_5-	C
7	$CH_3CH_2CH_2$-	C_6H_5-	C

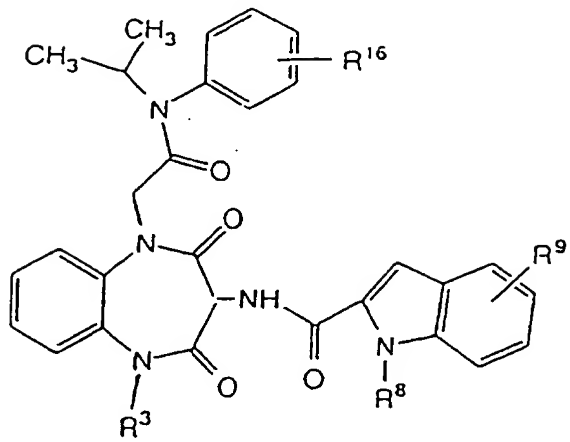
8	$CH_3CH_2CH_2CH_2$-	C_6H_5-	C
9	cyclohexyl	C_6H_5-	C
10	C_6H_5-	C_6H_5-	C
11	$(CH_3)_2CH$-	$C_6H_5CH_2$-	C
12	$(CH_3)_2CH$-	$(CH_3)_2CH$-	C



(B)

Table 2 (B)

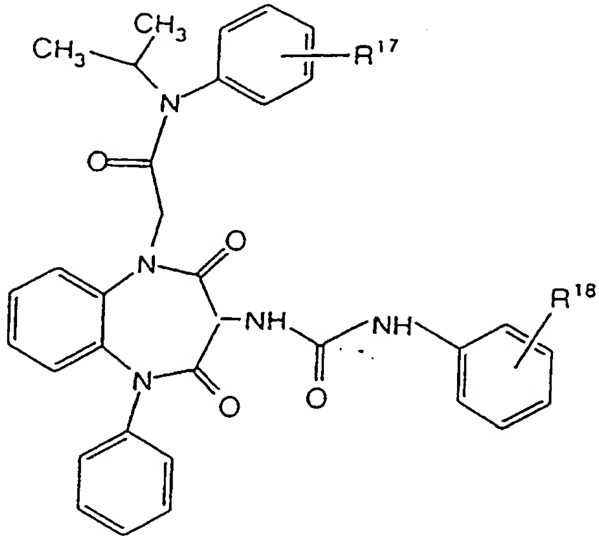
Compound	R^{13}	R^{14}	R^{15}	General Process
13	H	H	H	D
14	2-NH_2	4-Cl	H	D
15	2-NH_2	H	H	D
16	2-NH_2	4-F	H	D
17	2-COOH	H	H	D
18	3-COOH	H	H	D
19	2-OH	4-Cl	OCH_3	D
20	2-F	4-Cl	OCH_3	D
21	2-NH_2	4-Cl	OCH_3	D



(C)

Table 3 (C)

Compound	R^3	R^8	R^9	R^{16}	General Process
22	C_6H_5-	H	H	H	D
23	C_6H_5-	$-CH_2COOH$	H	H	E
24	C_6H_5	$-CH_2CH_2CH_2COOH$	H	H	E
25	C_6H_5-	H	5-OCH_3	H	D
26	C_6H_5-	$-CH_2COOH$	5-OCH_3	H	E
27	C_6H_5-	$-CH_2COOH$	5-Cl	H	E
28	C_6H_5-	H	5-CH_3	H	D
29	C_6H_5-	$-CH_2COOH$	5-CH_3	H	E
30	C_6H_5-	H	5-OH	H	D
31	C_6H_5-	H	7-NO_2	H	D
32	C_6H_5-	H	7-NH_2	H	D
33	C_6H_5-	H	H	OCH_3	D
34	C_6H_5-	H	H	$N(CH_3)_2$	D
35	C_6H_5-	H	H	morpholino	D
36	CH_3	H	H	H	D
37	CH_3	$-CH_2COOH$	H	H	E
38	H	H	H	H	D
39	H	H	H	OCH_3	D

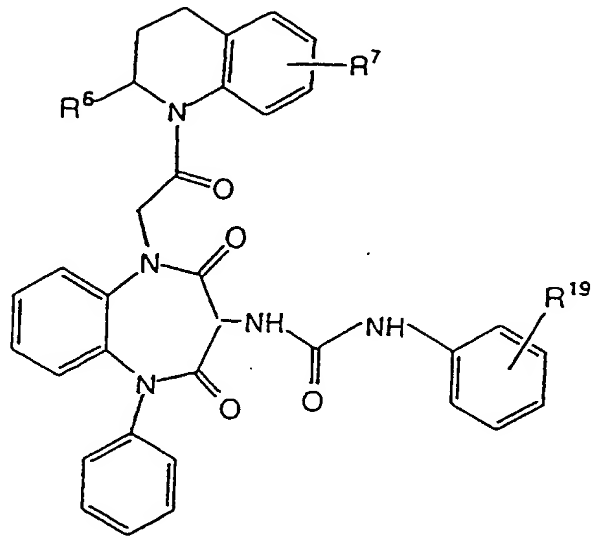


(D)

Table 4 (D)

Compound	R^{17}	R^{18}	General Process
40	H	3-OH	A
41	H	3-NH_2	A
42	H	3-tetrazolyl	A/B
43	H	3-$COOCH_2CH_3$	A
44	H	3-COOH	A
45	H	3-$NHSO_2CF_3$	A
46	H	3-OCH_3	A
47	H	3-SCH_3	A
48	H	3-$N(CH_3)_2$	A
49	H	3-$SOCH_3$	A
50	H	3-$SOOCH_3$	A
51	H	3-F	A
52	H	3-CH_2COOH	A
53	H	3-OCH_2COOH	A
54	4-OH	H	C
55	4-OCH_3	H	C
56	4-OCH_3	3-$COOCH_2CH_3$	A
57	4-OCH_3	3-COOH	A
58	4-$N(CH_3)_2$	H	C
59	4-$N(CH_3)_2$	3-OH	A
60	4-$N(CH_3)_2$	3-NH_2	A

61	4-morpholino	H	C
62	4-morpholino	COOH	C
63	4-$N(CH_3)_2$	3-$COOCH_2CH_3$	A
64	4-$N(CH_3)_2$	3-COOH	A

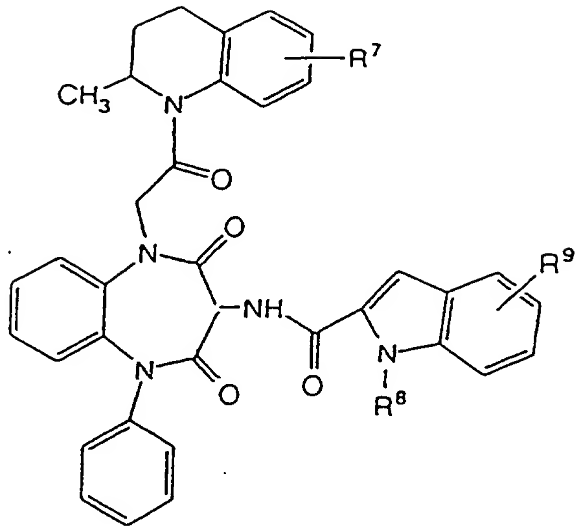


(E)

Table 5 (E)

Compound	R^6	R^7	R^{19}	General Process
65	H	H	H	C
66*	$-CH_3$	H	H	C
67*	$-CH_3$	H	H	C
68***	$-CH_3$	H	3-OH	A
69***	$-CH_3$	H	3-OH	A
70*'	$-CH_3$	H	3-COOH	A
71*'	$-CH_3$	H	3-COOH	A
72**'	$-CH_3$	6-F	H	C
73**'	$-CH_3$	6-F	H	C
74***'	$-CH_3$	6-OCH_3	H	C
75***'	$-CH_3$	6-OCH_3	H	C

* ** *** *' **' ***' denote pairs of diastereomers.

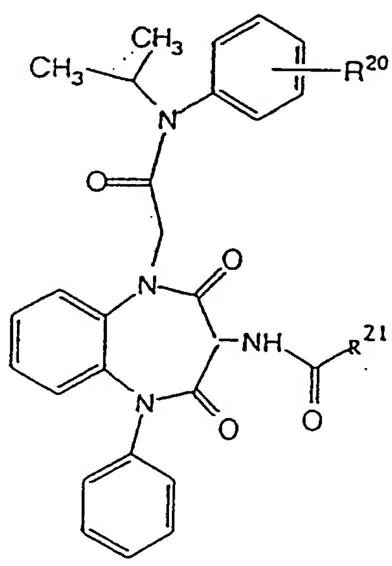


(F)

Table 6 (F)

Compound	R^7	R^8	R^9	General Process
76	H	H	H	D
77*	F	H	7-NH_2	D
78*	F	H	7-NH_2	D

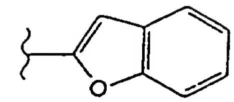
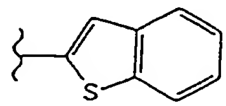
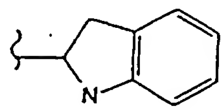
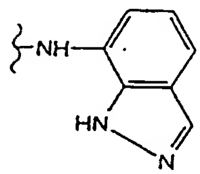
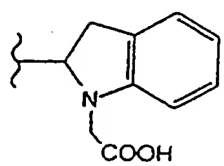
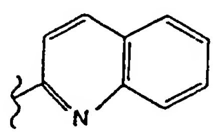
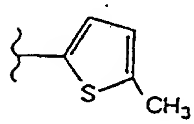
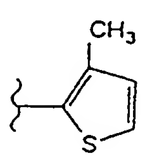
*, ** denotes pairs of diastereomers



(G)

Table 7 (G)

Compound	R^{20}	R^{21}	Synthesis Scheme

79	H		D
80	H		D
81	H		D
82	H		D
83	H		E
84	OCH_3		D
85	OCH_3		D
86	OCH_3		D

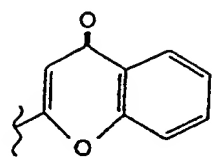
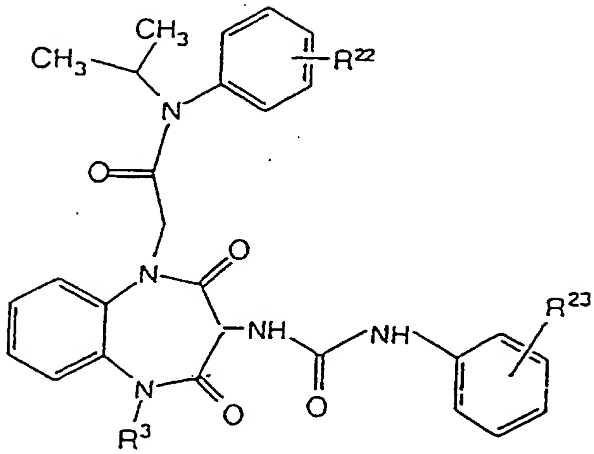
87	OCH_3		D

Table 8 (H)



(H)

Compound	R^{22}	R^{23}	R^3	Synthesis Scheme
88	H	H	CH_3	C
89	H	3-COOH	CH_3	A
90	H	3-COOH	H	A
91	H	2-OH	CH_3	A

GUINEA PIG GALL BLADDER ASSAY

Tissue Preparation:

Gallbladders were removed from guinea pigs sacrificed by cervical dislocation. The isolated gallbladders were cleaned of adherent connective tissue and cut into two rings from each animal (2-4 mm in length). The rings were subsequently suspended in organ chambers containing a physiological salt solution of the following composition (mM): NaCl (118.4); KCl (4.7); $MgSO_4 \times H_2O$ (1.2); $CaCl_2 \times 2H_2O$ (2.5); KH_2PO_3 (1.2); $NaHCO_3$ (25) and dextrose (11.1). The bathing solution was maintained at 37°C and aerated with 95% O_2/5%CO_2. Tissues were connected via gold chains and stainless steel mounting wires to isometric force displacement transducers (Grass, Model FT03 D). Responses were then recorded on a polygraph (Grass, Model 7E). One tissue from each animal served as a time/solvent control and did not receive test compound.

Assay:

Rings were gradually stretched (over a 120 min. period) to a basal resting tension of 1 gm which was maintained throughout the experiment. During the basal tension adjustment period, the rings were exposed to acetylcholine (ACH, 10^{-6} M) four times to verify tissue contractility. The tissues were then exposed to a submaximal dose of sulfated CCK-8 (Sigma, 3 X 10^{-9} M). After obtaining a stable response, the tissues were washed out 3 times rapidly and every 5 to 10 minutes for 1 hour to reestablish a stable baseline.

Compounds were dissolved in dimethylsulfoxide (DMSO) then diluted with water and assayed via a cumulative concentration-response curve to test compound (10^{-11} to 3 X 10^{-6} M) followed by a concentration-response curve to sulfated CCK-8 (10^{-10} to 10^{-6} M) in the presence of the highest dose of the test compound. As a final test, ACH (10 mM) was added to induce maximal contraction. A minimum of three determinations of activity were made for each test compound.

Table 10 set forth below lists experimental data for representative compounds of general Formula (I). Agonist activity in the guinea pig gall

bladder (GPGB) is listed as the % maximal contraction induced by acetylcholine (Ach) at a 30μM concentration of the test compound.

It will be appreciated by those skilled in the art that the compounds of the present invention can be administered therapeutically within the aforementioned dosage regimen up to without toxic effects as indicated by data which showed no toxic effects in rats even at dosages up to 12 mg/kg.

18-HOUR DEPRIVATION-INDUCED FEEDING PARADIGM

Male, Long-Evans rats (Charles River Co., Raleigh, NC), weighing 300-375 grams, were acclimated individually for at least a week in hanging, stainless steel mesh cages (17.8 X 25.4 X 17.8 cm high) with ad libitum access to water (delivered through automatic drinking spouts at the rear of the cage) and food (Lab Blox, Purina Rodent Laboratory Chow #5001) on a 12-hour light/dark cycle (lights on from 0600-1800 hours, or h) at approximately 22.8°C. Prior to testing, all chow, but not water, was removed at 1600 h. At 0900 h the next morning, rats were weighed. At 0945 h, rats were injected intraperitoneally (i.p.), orally (per os, or p.o.) or through an indwelling, intra-duodenal cannulea with a test compound or vehicle (2 ml/kg) and returned to their home cages. Food was presented at 1000 h. At 1030 h, remaining food and spillage was weighed.

GUINEA PIG GALL BLADDER ASSAY

Compound #	GPGB % Contraction (relative to Ach) 30μM
3	42%
6	66%
7	34%
9	43%
10	43%
13	46%
14	64%
15	55%
16	90%

17	49%
22	59%
23	73%
24	44%
25	26%
28	53%
30	44%
32	71%
33	55%
40	95%
41	81%
42	79%
44	83%
54	87%
55	70%
58	66%
59	92%
60	96%
64	90%
66	54%
67	78%
68	52%
69	83%
70	93%
71	98%
72	42%
73	62%
79	32%
82	88%
89	66%

Pharmacy Examples

Tablets

a.	Active ingredient	50mg
	Lactose anhydrous USP	163mg
	Microcrystalline Cellulose NF	69mg
	Pregelatinised starch Ph.Eur.	15mg
	Magnesium stearate USP	3mg
	Compression weight	300mg

The active ingredient, microcrystalline cellulose, lactose and pregelatinised starch are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

b.	Active ingredient	50mg
	Lactose monohydrate USP	120mg
	Pregelatinised starch Ph.Eur.	20mg
	Crospovidone NF	8mg
	Magnesium stearate USP	2mg
	Compression weight	200mg

The active ingredient, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and Crospovidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Capsules

a.	Active ingredient	50mg
	Pregelatinised Starch Ph.Eur.	148mg
	Magnesium stearate USP	2mg
	Fill weight	200mg

The active ingredient and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium

stearate (meshed through a 250 micron sieve). The blend is filled into hard gelatin capsules of a suitable size.

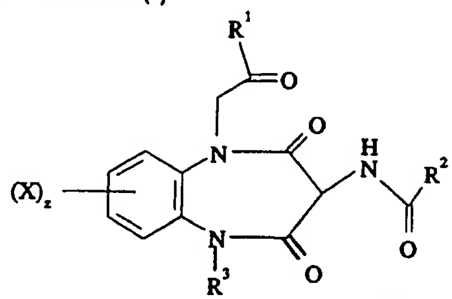
b.

Active ingredient	50mg
Lactose monohydrate USP	223mg
Povidone USP	12mg
Crospovidone NF	12mg
Magnesium stearate	3mg
Fill weight	300mg

The active ingredient and lactose are blended together and granulated with a solution of Povidone. The wet mass is dried and milled. The magnesium stearate and Crospovidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is filled into hard gelatin capsules of a suitable size.

We claim:

1. A compound of Formula (I)

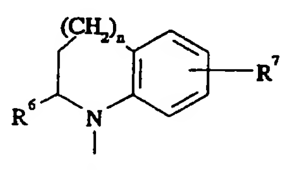


(I)

and physiologically salts and solvate thereof wherein:

X is either hydrogen, trifluoromethyl, alkyl, C_{1-4}alkylthio, -O(C_{1-4}alkyl) or halogen;

R^1 is either Formula II or $-NR^4R^5$.;



(II)

R^2 is either:

(1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrole, indole, benzofuran, thiophene, benzothiophene, indoline, quinoline or 4-oxobenzopyran and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R^8 as defined hereunder and said indole, indoline, quinoline, benzofuran, benzothiophene or 4-oxo-benzopyran may optionally be substituted in the benzo ring thereof by the group R^9 as defined hereunder or

(2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, -O(C_{1-4}alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino, dimethylamino, -NHR^{10}, 1-pyrrolidinyl or tetrazolyl; or

(3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C_{1-4} alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino or dimethylamino; or

(4) -NHR^{11} where R^{11} is defined hereinunder or R^{11} is 7-indazolyl containing a group R^{10} at the N-1 position;

R^3 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl mono- or disubstituted independently with halogen;

R^4 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, phenyl, -(CH_2)$_p$CN or -(CH_2)$_p$COO(C_{1-4}alkyl) and R^5 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6} alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with C_{1-3}alkyl, cyano, hydroxy, dimethylamino, -O(C_{1-4}alkyl), -O($CH_2C_6H_5$), -NH(C_{1-4}alkyl), -COO(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$ pyrrolidino, morpholino or halogen or R^4 is C_{1-2}alkyl and R^5 is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;

R^6 is hydrogen or methyl;

R^7 is hydrogen, hydroxy, fluoro, dimethylamino, -O(C_{1-4}alkyl) or -O($CH_2C_6H_5$);

R^8 is -(CH_2)$_b$COOH;

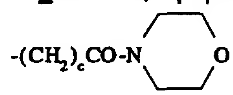
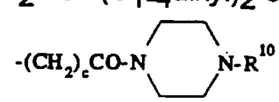
R^9 is methyl, chloro, nitro, hydroxy, methoxy or -NHR^{10};

R^{10} is hydrogen, acetyl, C_{1-4}alkyl, -SO_3H, -SO_2CH_3, -SO_2CF_3 or -$SO_2C_6H_5$, C_{1-4}alkoxycarbonyl;

R^{11} is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C_{1-4}alkylthio, -(CH_2)$_c$COOH, -(CH_2)$_c$COO(C_{1-4}alkyl), -(CH_2)$_c$$SCH_3$, -($CH_2$)$_c$$SOCH_3$, -($CH_2$)$_c$$SO_2CH_3$, -($CH_2$)$_c$$CONH_2$, -$SCH_2$COOH, -CONH($SO_2CH_3$), -CONH($SO_2CF_3$), -($CH_2$)$_c$N($C_{1-4}$alkyl)$_2$,

$-(CH_2)_cNH(SO_2CF_3)$, $-(CH_2)_cN(SO_2CF_3)(C_{1-4}alkyl)$, $-(CH_2)_cSO_2NHCO(C_{1-4}alkyl)$, $-(CH_2)_cSO_2N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $-(CH_2)_cCONHSO_2(C_{1-4}alkyl)$, $-(CH_2)_cCON(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-(CH_2)_cOR^{12}$ $-(CH_2)_cNHR^{10}$ or phenyl monosubstituted with $-(CH_2)_c$(tetrazolyl), $-(CH_2)_c$(carboxamidotetrazolyl) or $-(CH_2)_c$(pyrrolidinyl) or R^{11} is selected from pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, $-O(C_{1-4}$ alkyl), amino, dimethylamino, $-NHR^{10}$;

R^{12} is hydrogen, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $-CH_2C_6H_5$, $-CH_2COOH$, $-CH_2CONH_2$, $-CH_2CONH(C_{1-4}alkyl)$, $-CH_2CON(C_{1-4}alkyl)_2$ or


or


z is 1 or 2;

n is 1 or 2;

p is an integer from 1-4;

b is an integer from 0-3; and

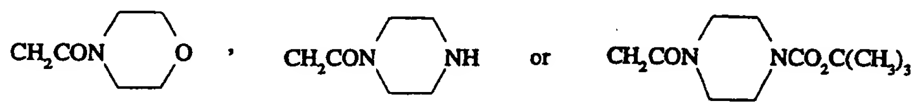
c is 0 or 1.

2. A compound according to Claim 1 wherein R^1 represents the group of Formula (II) wherein R^6 is methyl, R^7 is hydrogen, hydroxyl, methoxy or fluorine and n is 1 or R^1 represents the group NR^4R^5 wherein R^4 represents C_{3-6} alkyl, cyclohexyl or phenyl, and R^5 represents C_{3-6} alkyl or phenyl optionally substituted in the para position by hydroxy, dimethylamino, methoxy, fluorine, pyrrolidino or morpholio.

3. A compound according to Claims 1 or 2 wherein R^1 represents the group NR^4R^5 and R^4 represents propyl or isopropyl and R^5 represents phenyl or phenyl substituted in the para position by a group selected from hydroxy, methoxy, dimethylamino, fluorine, or morpholino.

4. A compound according to any of Claims 1 to 3 wherein R^2 represents a group selected from phenyl (optionally substituted by one or two groups

which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxy,) or NHR^{11} wherein R^{11} is phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C_{1-4} alkoxycarbonyl, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein R^{12} represents hydrogen, methyl, benzyl, CH_2CO_2H, CH_2CONH_2, $CH_2CONHCH_3$, $CH_2CON(CH_3)_2$



)or 7-indazolyl wherein the N-1 substituted is hydrogen, or R^2 represents an indole group wherein the nitrogen atom is optionally substituted by the group $-CH_2CO_2H$ and the benzo ring is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

5. A compound according to any of Claims 1-4 wherein R^2 represents an indole group which is unsubstituted on the nitrogen atom and in which the benzo ring thereof is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

6. A compound according to any of Claims 1-5 wherein R^3 represents hydrogen, methyl, cyclohexyl,2-fluorophenyl or phenyl.

7. A compound according to any of Claims 1-6 wherein R^3 represents phenyl.

8. A compound according to any of Claims 1-7 wherein X represents hydrogen.

9. A compound of Formula (I) wherein R^1 represents NR^4R^5 and R^4 represents isopropyl and R^5 represents p-methoxyphenyl; R^2 represents an unsubstituted 2-indole group; R^3 represents phenyl and X represents hydrogen and enantimers thereof.

10. A compound according to any of Claims 1 to 9 for use in therapy.

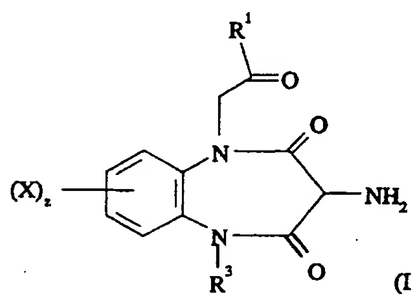
11. The use of a compound according to any of Claims 1 to 9 in the manufacture of a medicament for th treatment of conditions where a modulation of the affects gastric or CCK is of therapeutic benefit.

12. A method of treatment of a mammal including man for conditions where modulation of the effects of gastric and/or CCK is of a therapeutic benefit comprising administration of an effective amount of a compound according to any of Claims 1 to 9.

13. A pharmaceutical composition comprising a compound according to any of Claims 1 to 9 in an admixture with one or more physiologically acceptable carriers or excipients.

14. A process for the preparation of compounds as defined in Claim 1 which comprises:

(a) reacting a compound of Formula (III) wherein R^1, R^3, X and z are as defined in Formula (I)

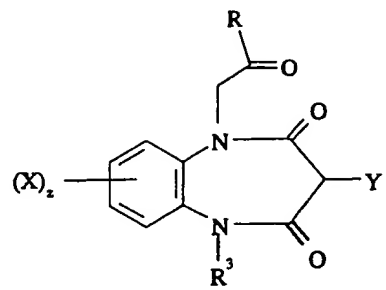


(III)

with a compound $R^{11}Y$ (IV) wherein Y is the group -NCO, HNCOCl or $NHCOR_a$ where R_a is nitro substituted phenoxy group or a 1-imidazole group.

wherein R^{11} has the meaning defined in Formula (I) or is a group convertible thereto.

(b) reacting a compound of Formula (V)



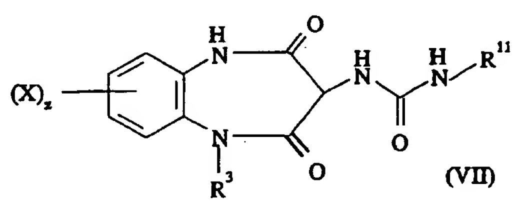
(V)

wherein R^1, R^3 X and z have the meaning defined above and wherein Y is the group -NCO, -NHCOCl or $NHCOR_a$ wherein R_a is a nitro substituted phenoxy group or a 1-imidazole group with an amine (VI)

$$H_2N\text{-}R^{11} \qquad \text{(VI)}$$

wherein R^{11} has the meaning defined in Formula (I) and is a group convertible thereto.

(c) reacting a compound of Formula (VII) wherein. R^3 , R^{11} and X are as defined in Formula (I)

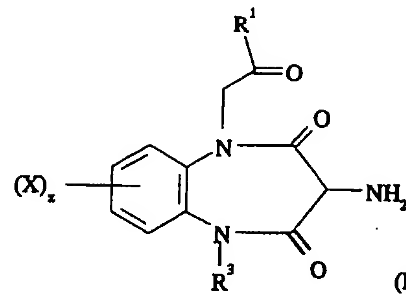


(VII)

with the compound of Formula (VIII) wherein R^1 has the meanings defined in Formula (I)

$$R^1COCH_2hal \qquad \text{(VIII)}$$

(d) reacting a compound of Formula (III) wherein R^1, R^3 X and Z are as defined in Formula (I).



(III)

with an acid of Formula (IX) or an activated deviative thereof.

$$HOOC\text{-}R^2 \quad (IX)$$

wherein R^2 has the meanings defined in Formula (I) or is a group convertible thereto;

and thereafter, if necessary or desired, converting the required compound into another compound of the invention.

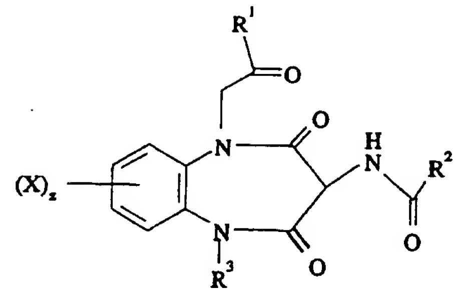
15. A method of treating obesity and related disease states in a mammal which comprises administering to said mammal a therapeutically-effective amount of a compound according to Claim 1, whereby an anorectic effect is achieved in said mammal.

16. A method for modifying the food intake of a mammal which comprises administering to said mammal a therapeutically-effective amount of a compound according to Claim 1, whereby food intake is modified.

17. A method for inducing satiety in mammal which comprises administering to said mammal a therapeutically-effective amount of a compound according to Claim 1, whereby satiety is induced.

18. A method for providing appetite regulation in mammal which comprises administering to said mammal a therapeutically-effective amount of a compound according to Claim 1, whereby appetite regulation is achieved.

19. A compound of Formula (I)

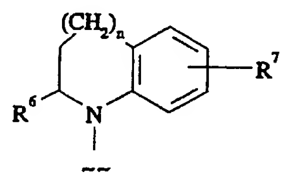


(I)

and physiologically salts and solvate thereof wherein:

X is either hydrogen, trifluoromethyl, alkyl, C_{1-4}alkylthio, -O(C_{1-4}alkyl) or halogen;

R^1 is either Formula II or $-NR^4R^5$.;



(II)

R^2 is either:

(1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrole, indole, benzofuran or indoline and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R^8 as defined hereunder and said indole, indoline or benzofuran, may optionally be substituted in the benzo ring thereof by the group R^9 as defined hereunder or

(2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, -O(C_{1-4}alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino, dimethylamino, $-NHR^{10}$, 1-pyrrolidinyl or tetrazolyl; or

(3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C_{1-4} alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino or dimethylamino; or

(4) $-NHR^{11}$ where R^{11} is defined hereinunder or R^{11} is 7-indazolyl containing a group R^{10} at the N-1 position;

R^3 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl mono- or disubstituted independently with halogen;

R^4 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, phenyl, $-(CH_2)_pCN$ or $-(CH_2)_pCOO(C_{1-4}alkyl)$ and R^5 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6} alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with C_{1-3}alkyl, cyano, hydroxy, dimethylamino, $-O(C_{1-4}alkyl)$, $-O(CH_2C_6H_5)$, $-NH(C_{1-4}alkyl)$, $-COO(C_{1-4}alkyl)$, pyrrolidino or halogen or R^4 is C_{1-2}alkyl and R^5 is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;

R^6 is hydrogen or methyl;

R^7 is hydrogen, hydroxy, fluoro, dimethylamino, $-O(C_{1-4}alkyl)$ or $-O(CH_2C_6H_5)$;

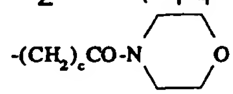
R^8 is $-(CH_2)_bCOOH$;

R^9 is methyl, chloro, nitro, hydroxy, methoxy or $-NHR^{10}$;

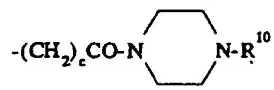
R^{10} is hydrogen, C_{1-4}alkyl, $-SO_3H$, $-SO_2CH_3$, $-SO_2CF_3$ or $-SO_2C_6H_5$;

R^{11} is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C_{1-4}alkylthio, $-(CH_2)_cCOOH$, $-(CH_2)_cCOO(C_{1-4}alkyl)$, $-(CH_2)_cSCH_3$, $-(CH_2)_cSOCH_3$, $-(CH_2)_cSO_2CH_3$, $-(CH_2)_cCONH_2$, $-SCH_2COOH$, $-CONH(SO_2CH_3)$, $-CONH(SO_2CF_3)$, $-(CH_2)_cN(C_{1-4}alkyl)_2$, $-(CH_2)_cNH(SO_2CF_3)$,$-(CH_2)_cN(SO_2CF_3)(C_{1-4}alkyl)$, $-(CH_2)_cSO_2NHCO(C_{1-4}alkyl)$, $-(CH_2)_cSO_2N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $-(CH_2)_cCONHSO_2(C_{1-4}alkyl)$, $-(CH_2)_cCON(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-(CH_2)_cOR^{12}$ $-(CH_2)_cNHR^{10}$ or phenyl monosubstituted with $-(CH_2)_c$(tetrazolyl), $-(CH_2)_c$(carboxamidotetrazolyl) or $-(CH_2)_c$(pyrrolidinyl) or R^{11} is selected from pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, $-O(C_{1-4}$ alkyl), amino, dimethylamino, $-NHR^{10}$;

R^{12} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2C_6H_5$, $-CH_2COOH$, $-CH_2CONH_2$, $-CH_2CONH(C_{1-4}$alkyl), $-CH_2CON(C_{1-4}$alkyl$)_2$ or



or



z is 1 or 2;

n is 1 or 2;

p is an integer from 1-4;

b is an integer from 0-3; and

c is 0 or 1.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/EP 94/01131

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07K5/02 C07K5/06 C07K5/08 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 376 849 (ROUSSEL-UCLAF) 4 July 1990 cited in the application see claims; example 2 ---	1,4-8, 10-14
P,X	WO,A,93 14074 (GLAXO SPA) 22 July 1993 see claims; example 15 ---	1,10-13
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 34, no. 11 , November 1991 , WASHINGTON US pages 3350 - 3359 J.F. KERWIN ET AL. 'Cholecystokinin Antagonists: (R)-Tryptophan-Based Hybrid Antagonists of High Affinity and Selectivity for CCK-A Receptors' see the Introduction on pages 3350-3353 see figure I --- -/--	1,5, 10-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 1994	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

INTERNATIONAL SEARCH REPORT

Inte[illegible]onal Application No
PCT/EP 94/01131

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 487 207 (MERCK & CO. INC.) 27 May 1992 see claims; examples -----	1,10-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 94/01131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark : Although claim 12 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. [ ] Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte... ...onal Application No
PCT/EP 94/01131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0376849	04-07-90	FR-A- 2641280	06-07-90
		JP-A- 2215774	28-08-90
		US-A- 4988692	29-01-91
WO-A-9314074	22-07-93	AU-A- 3193593	22-07-93
		AU-B- 3450193	03-08-93
		CA-A- 2087672	22-07-93
		CN-A- 1074678	28-07-93
		EP-A- 0558104	01-09-93
EP-A-0487207	27-05-92	US-A- 5206234	27-04-93
		JP-A- 5105667	27-04-93